ROLE OF DIFFUSION TENSOR IMAGING IN MESIAL TEMPORAL LOBE EPILEPSY

A THESIS SUBMITTED TO THE BABA FARID UNIVERSITY OF

HEALTH SCIENCES, FARIDKOT (PUNJAB)

FOR THE AWARD OF DEGREE OF

DM

IN

NEUROLOGY

BY

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DECLARATION

I declare that the thesis entitled **"ROLE OF DIFFUSION TENSOR IMAGING IN MESIAL TEMPORAL LOBE EPILEPSY"** has been prepared by me under the guidance of **Dr. Gagandeep Singh**, Professor & Head, Department of Neurology, Dayanand Medical College and Hospital, Ludhiana. No part of this thesis has formed the basis for the award of any degree previously.

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Dedicated

to

my family

&

teachers

ACKNOWLEDGEMENT

First and foremost, I would like to express my sincere gratitude to my teacher and my guide Prof. Gagandeep Singh for his continuous support in my thesis study. Without his guidance and dedicated involvement in every step throughout the process, this thesis would not have been possible. His teaching style and enthusiasm for the topic made a strong impression on me. I could not have imagined having a better research supervisor and mentor for my thesis study.

Besides my research supervisor, I would like to thank Dr. Kavita Saggar and Dr. Monika Singla, for their insightful comments and encouragement. They raised many precious points in our discussion and I hope that I have managed to address several of them here.

I would also like to show gratitude to my teachers, Dr. Birinder S Paul and Dr. Rajinder Bansal for their valuable support and understanding.

Getting through my thesis study required more than academic support, and I cannot begin to express my gratitude and appreciation for their friendship – my colleagues at DMCH and the neurology department staff and with the able guidance of Mrs Namita, Mr. Naveen Bhatia, who has helped me with the statistic work and has swiftly replied to every problem.

Most importantly, none of this could have happened without my family. To my parents, who always offered their encouragement through phone calls and loving prayers for me. To my grandparents, my sisters and my better-half, Dr Varsha Arla, you all were always there even at odd hours to talk to me and solve any problem.

Dr. Sajja Venkatesh

ABSTRACT

Introduction: Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy which is surgically remediable. Mesial temporal lobe sclerosis (MTS) is the major underlying cause of TLE. Diffusion Tensor Imaging (DTI) provides insight into the white matter microstructure and is a non-invasive MRI technique. In TLE widespread DTI abnormalities have been reported. Although conventional MRI only shows unilateral involvement of the hippocampal sclerosis in TLE patients, DTI was found to be useful in demonstrating the widespread involvement of other regions of brain as well.

Aim and Objectives: We aimed to study this hypothesis by analysing DTI parameters (Fractional Anisotropy and Mean Diffusivity) in various areas of the brain in unilateral TLE patients.

Material and methods: We prospectively evaluated 16 patients with unilateral TLE by using DTI, MRI, clinical and EEG parameters and compared with 14 healthy controls. Of these 8 were Right sided and 8 were left sided TLE patients. We compared the mean diffusivity (MD) and fractional anisotropy (FA) from symmetrical voxels by sampling the following areas namely hippocampus, parahippocampal gyrus, caudate, thalamus, external capsule, anterior and posterior cingulate gyrus, optic radiation, fornix, uncinate fasciculus, arcuate fasciculus, superior and inferior longitudinal fasciculus and inferior fronto-occipital fasciculus. We compared the differences of these DTI measurements between patients and controls.

Results: There was statistically significant decrease in FA values with increased mean diffusivity in multiple regions/tracts (hippocampus, parahippocampus, thalamus, external capsule, posterior cingulate gyrus, fornix, uncinate and arcuate fasciculi and inferior longitudinal fasciculus), which were seen in temporal as well as extratemporal areas predominantly on the side ipsilateral to the focus of seizure in EEG and MRI.

Conclusion: DTI is highly sensitive to cortical and sub-cortical white matter micro structural changes that underlie epilepsy. DTI is an important radiological tool in the pre surgical evaluation and planning of temporal lobe epilepsy as asymmetrically decreased fractional anisotropy (FA) or increased mean diffusivity (MD) can be a useful clue in lateralization of seizure focus.

Key Words: Diffusion tensor imaging, temporal lobe epilepsy.

LIST OF ABBREVIATIONS

3D TFE	-	3D turbo field echo
ACG	-	Anterior cingulate gyrus
ADC	-	Apparent diffusion coefficient
AF	-	Arcuate fasciculus
DTI	-	Diffusion tensor imaging
DWI	-	Diffusion weighted imaging
EC	-	External capsule
EEG	-	Electroencephalography
FA	-	Fractional anisotropy
FLAIR	-	Fluid attenuated inversion recovery
GTCS	-	Generalized tonic-clonic seizures
HS	-	Hippocampal sclerosis
IFO	-	Inferior fronto-occipital fasciculus
ILAE	-	International League Against Epilepsy
ILF	-	Inferior longitudinal fasciculus
IR	-	Inversion recovery
MD	-	Mean diffusivity
MRI	-	Magnetic resonance imaging
MTLE	-	Mesial temporal lobe epilepsy
MTS	-	Mesial temporal sclerosis
PCG	-	Posterior cingulate gyrus
PHG	-	Parahippocampal gyrus
ROI	-	Region of interest
SLF	-	Superior longitudinal fasciculus

SPM	-	Statistical parametric mapping
T1/T2W	-	T1/T2 weighted
TLE	-	Temporal lobe epilepsy
UF	-	Uncinate fasciculus

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Introduction

A seizure is defined as the signs and/or symptoms caused by the abnormal excessive synchronous neuronal activity in the brain[1]. Epilepsy is the tendency to have unprovoked seizures. About 1% of people worldwide are suffering from epilepsy.

According to the International League Against Epilepsy (ILAE) official report in 2014, epilepsy should be considered in any of the following conditions: two or more seizures occurring >24 hours apart, one unprovoked seizure and a probability of recurrent seizure risk over 60%, and diagnosis of an epilepsy syndrome[2]. If there is any epileptiform discharge on electroencephalography, or a potential epileptogenic structure on brain imaging, the probability of recurrent epileptic seizure exceeds 60%[3].

The term Temporal lobe epilepsy (TLE) was included in the classification of the ILAE in 1989 under the group of “localization-related symptomatic epilepsies characterized by seizures with specific modes of precipitation”[4].

In human brain, most epileptogenic area is the temporal lobe. Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy in adulthood. It is estimated that it represents about 40% of all epilepsies in adult people[5].

The common clinical symptoms during seizure episode includes staring look and lack of responsiveness, often associated with automatisms of mouth or hand. They represent about 2/3rd of intractable seizure population requiring surgical management[6].

Among such patients, mesial temporal sclerosis (MTS, also called hippocampal sclerosis) is the most common underlying pathologic abnormality (>80%), as has been demonstrated in both autopsy and post resection studies. Other etiologies include malformations of cortical development, mass lesions, AV malformations, gliosis etc[7].

Although mesial temporal sclerosis (MTS) has long been recognized in association with temporal lobe epilepsy (TLE), there is a growing evidence from electroclinical data that, epileptogenic onset zone, i.e., the medial temporal lobe, is expanded to incorporate a larger epileptic network, i.e., larger cortical or subcortical regions involved in seizure propagation or in seizures control[8].

Numerous neuroimaging studies demonstrated that structural or functional abnormalities (metabolic or subtle structural lesions) may extend beyond the seizure onset zone in unilateral MTLE[9,10,11].

DTI studies have demonstrated extensive bilateral white matter abnormalities in TLE that extend far beyond the temporal lobe, even in patients with unilateral MTS. These widespread changes may be reflected as altered diffusion tensor imaging metrics like Fractional Anisotropy (FA) & Mean Diffusivity (MD) i.e., Apparent Diffusion Coefficient (ADC)[12].

Diffusion weighted imaging was introduced in 1986 by Le Bihan et al. Since then, diffusion MRI has been extraordinarily successful. Its main clinical application has been in the study and treatment of neurological disorders[13]. By introducing directionality into diffusion weighted images, diffusion tensor images are obtained. It assesses the molecular and biochemical environment of cerebral tissue noninvasively and is capable of demonstrating microstructural alterations in a variety of disorders[14].

Diffusion tensor imaging (DTI) can reveal abnormalities in white matter fiber structure and can provide models of brain connectivity and is now rapidly becoming a standard for the radiological assessment of white matter disorders[15].

Diffusion tensor imaging metrics such as fractional anisotropy (FA) and mean diffusivity (MD) i.e., apparent diffusion coefficient (ADC) and tractography are used in depicting the relationship of CNS mass lesions to adjacent white matter tracts for presurgical evaluation. Diffusion tensor imaging metrics have also been used to differentiate solitary metastasis from gliomas[12].

To date, there are many diffusion tensor imaging studies in the hippocampus and extra temporal grey and white matter in patients with temporal lobe epilepsy. However, the results are variable[16].

We have intended to explore the utility of diffusion tensor imaging in temporal lobe epilepsy and depict the focal and widespread abnormalities that occur in temporal lobe epilepsy cases in our population. The study might establish the diagnostic value of diffusion tensor imaging in epilepsy and incorporate it in routine protocol.

Aims and Objectives

To study the Fractional Anisotropy and Mean Diffusivity of both hippocampi and various white matter tracts in

(i) Patients with unilateral temporal lobe epilepsy diagnosed with clinical and EEG features, with or without MRI showing unilateral hippocmpal sclerosis,

(ii) Normal controls

Review of Literature

We identified articles through searches of PubMed, Science Direct, and Embase with use of the search terms “Diffusion tensor Imaging (DTI)”, “Temporal Lobe Epilepsy (TLE)” separately, and in combination with “review articles”. We also identified papers from the authors’ own files and from references cited in relevant articles. We generated the final reference list on the basis of articles’ relevant to the topic of this Personal View.

Mesial Temporal Lobe Epilepsy

Temporal lobe epilepsy (TLE) is the most common form of adult localization-related epilepsy and also the most common form of surgically remediable focal epilepsy, accounting for 60–75% of patients undergoing surgery for medically refractory epilepsy. Mesial temporal lobe sclerosis (MTS) is the major underlying cause of MTLE, and it is present in 60-70% of patients with MTLE who undergo surgery for treatment of medically refractory seizures[17].

Jackson in the 19th Century was the first to link seizures characterized by a “dreamy state” to lesions near the uncus in the temporal lobe (hence the term “uncinate fits”)[18]. Gibbs and Lennox suggested the term psychomotor epilepsy to describe a characteristic EEG pattern together with emotional, mental, and autonomic phenomena for seizures originating in the temporal lobe[19]. Gastaut proposed the term CPSs for partial onset seizures associated with loss of consciousness[4].

MTLE (mesial temporal lobe epilepsy) is defined as a symptomatic focal epilepsy that can be subcategorized as limbic epilepsy (versus neocortical epilepsy). The revised ILAE (The International League Against Epilepsy) classification defines MTLE as a “distinctive constellation/ electroclinical syndrome” with the most common pathological substrate being hippocampal sclerosis (HS)[20]. MTLE is often associated with hippocampal sclerosis; lesional temporal lobe epilepsy due to specific identifiable lesions localized to areas that preferentially project to mesial

temporal structures; and cryptogenic temporal lobe epilepsy, for which no etiology can be determined[21]. MTLE has been associated with widespread white mater (WM) alternations in addition to mesial temporal sclerosis (MTS)[22].

MTLE-HS has a distinct clinical presentation called “limbic seizure” resulting from epileptic activity within the limbic structures; however, they are not distinguishable from MTLE with other pathologies than HS. MTLE-HS also has specific electrographic features, neuroimaging, and pathological findings. The term hippocampal sclerosis denotes a specific pattern of cell loss mostly involving CA1 and hilar neurons and least the CA2 region[23]. MTLE with HS has a poor prognosis with medical treatment, however, many of these patients have excellent response to surgery and removal of the epileptogenic zone. One prospective study found that surgery was clearly superior to medical therapy in this population of patients[24].

Epidemiology of MTLE

Epidemiological studies in TLE are few. Hauser and Kurland provided the best available epidemiological data on TLE, the incidence rate was 10.4 per 100.000 and the prevalence was 1.7 per 1000 people[25]. In epilepsy centers the TLE prevalence usually is 60-70%. The higher rates of TLE observed in epilepsy centers are probably related with its intractability[26].

Temporal lobe epilepsy is usually diagnosed in the first two decades of life, and has no sexual predilection, although females may experience catamenial seizures[27]. Mesial temporal sclerosis is a major etiology for epilepsy in adult populations, but it has been reported to be an uncommon finding in children with epilepsy[28].

Typically, when MTLE-HS is diagnosed, a typical course of the disease can be retrospectively recognized, including early prolonged febrile seizures, a latent period, onset in mid-to-late childhood, auras that may initially occur in isolation, periods of seizure remission during adolescence or early adulthood. Then the condition progresses,

associating elaborated seizures, progressive drug-resistance and cognitive, mainly memory, disorders of variable intensity[29]. The semiological features of MTLE were said to include typical auras such as rising epigastric sensations, déjà vu, affective phenomena (fear or sadness), or experiential phenomena followed by unilateral motor signs (frequently ipsilateral contraction of face or mouth, head deviation) and bilateral motor phenomena in the face or axial muscles. Behavioural arrest and oral automatisms are common and bitemporal spread heralds alteration in consciousness, amnesia, autonomic phenomena (change in heart rate and respirations), and prominent motor automatisms (tonic and dystonic posturing)[30]. The seizures have a relatively gradual onset/offset, developing over 1-2minutes, with partial awareness at the onset, and lasting for 2 to 10minutes. Auras are common, with visceral, autonomic, psycho-affective, experiential components, presenting less frequently diverse sensory or sensorial symptoms. Awareness is generally preserved at onset, but then loss of consciousness occurs, with initial motionless stare, and automatisms, which typically are oro-alimentary, vocal or gestural, accompanied by motor signs such as contralateral dystonic posturing.[23]

ANATOMY OF WHITE MATTER TRACTS:

Anatomy of the limbic system[31]:

Limbic lobe is phylogenetically older cortex and contains few layers than the neocortex. It plays a major role in memory, olfaction and emotion. It is composed of the hippocampus, the parahippocampal gyrus, dentate gyrus, subiculum, cingulate gyrus and the subcallosal area. Limbic system consists of the limbic lobe and some subcortical structures like the amygdala, mammillary bodies and the septal nuclei.

The limbic lobe consists of three arches surrounding the diencephalon and the basal ganglia.

The outer arch extends from the temporal to frontal lobes and consists of the uncus, parahippocampal gyrus, cingulate gyrus and the

subcallosal area. The middle arch consists of the hippocampus proper (ammons horn), dentate gyrus, indusium greiseum and the paraterminal gyrus. The inner arch is the smallest and consists of fornix and fimbria, and extends from the temporal lobes to mamillary bodies.

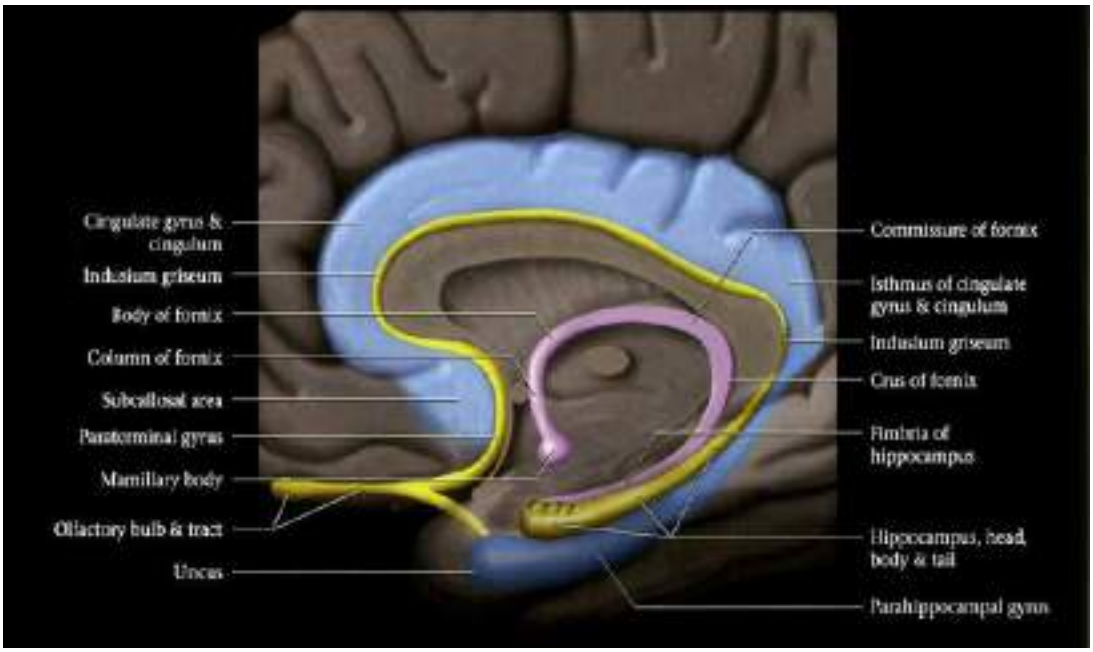


Figure 1: Diagrammatic representation of the limbic system

Imaging anatomy[31]:

Hippocampus lies on the medial aspect of temporal lobe and bulges into floor of the temporal horn. It consists of two interlocking U-shaped grey matter structures, the hippocampus proper or the Ammons horn and the dentate gyrus. It has a head which consists of 3-4 digitations on the superior surface, a cylindrical body oriented parasagitally, and a tail. The Ammons horn continues laterally into the subiculum. Subiculum is the transition into the parahippocampal gyrus or the entorhinal cortex, which is part of the neocortex. A thin layer of white matter covers the hippocampus called alveus, which consists of the efferent fibres continuing as the fimbria and fornix.

Amygdala is a large grey matter nucleus which is situated anterior and superior to the hippocampus, lateral to uncus. Uncinate gyrus connects amygdala to the hippocampus.

The fimbria thickens posteriorly and splits off from the hippocampus to form the crus. The crus of the fornix attaches to the anterior surface of the splenium of corpus callosum. The crura of both sides unite to form the hippocampal commisure, and continues anteriorly as the body.

Figure 2: Coronal diagrammatic representation of the hippocampus

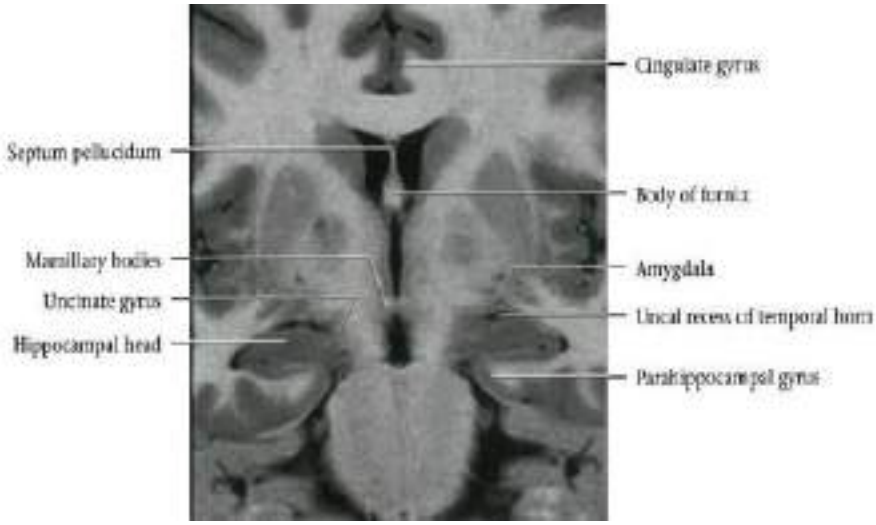


Figure 3: Coronal T1 IR image at the level of hippocampal head

Connections of the hippocampus[32]:

The hippocampus is directly connected to the parahippocampal gyrus through the subiculum, and to the amygdala through the uncinate gyrus. Two major hippocampal pathways are the fornix and the parahippocampal gyrus.

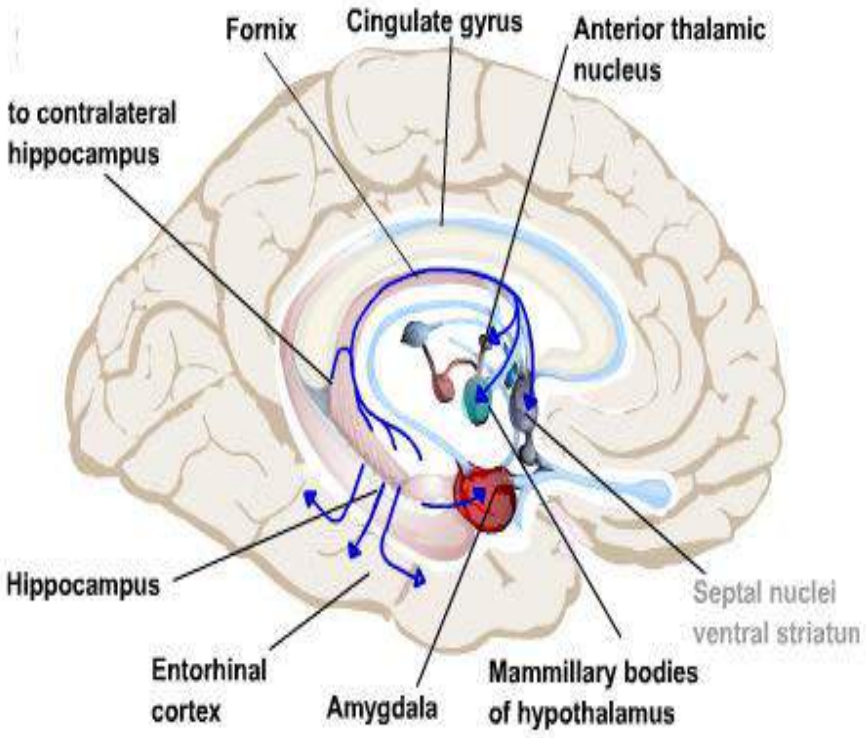


Figure 4: Output pathways of the hippocampus

The crus of fornix contacts the contralateral fornix and forms the hippocampal commissure, through which bilateral hippocampi connect with each other. They then continue as body of fornix to the anterior commissure where it splits into three parts.

1. Precommissural fornix, just before the commissure which goes to the septal nuclei, preoptic nuclei, orbital cortex, anterior cingulate cortex and the ventral striatum.
2. Anterior commissure, the second pathway connecting bilateral hippocampi.
3. Post commissural fornix going to mammillary bodies and the anterior nucleus of the thalamus. Anterior thalamic nuclei connect to the cingulate cortex.

The cingulate cortex in turn projects to the entorhinal cortex or the parahippocampal gyrus, completing the Papez circuit. The Papez circuit is involved in learning, memory, emotion and social behaviour.

Parahippocampal gyrus is a major source of input to the hippocampus. The cingulate gyrus, neocortex, amygdala, orbital cortex and the olfactory bulb have inputs through the parahippocampal gyrus to the hippocampus.

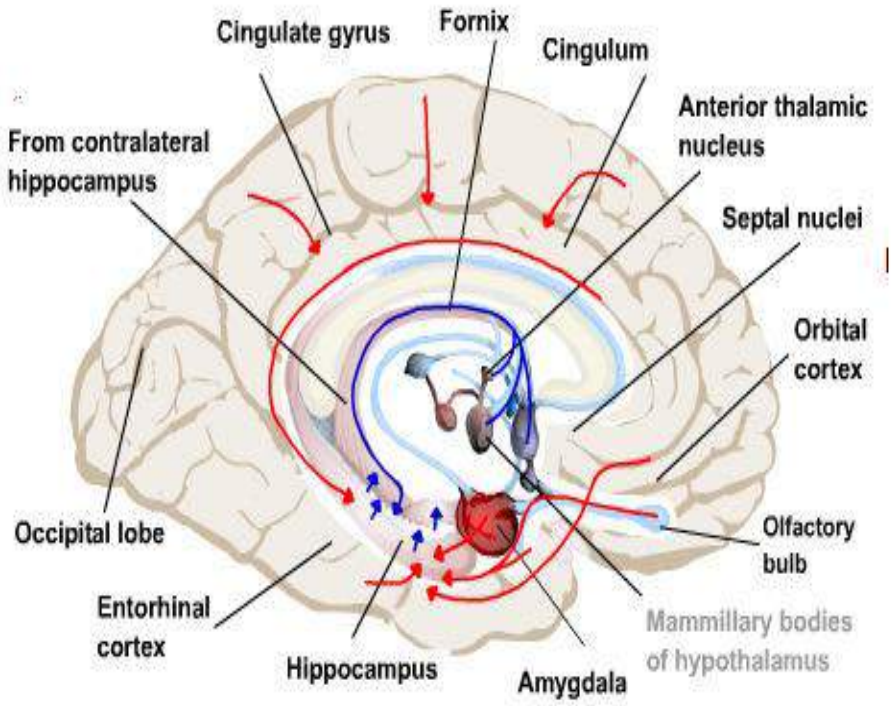


Figure 5: Input pathways of the hippocampus

ASSOCIATION FIBRES: Association fibres connect cortical areas within a hemisphere.

Cingulum:

It arches over the corpus callosum. It starts beneath the rostrum of corpus callosum

in the parolfactory area, courses in the cingulate gyrus, extends posteroinferiorly

into the parahippocampal gyrus and the uncus connecting the frontal, parietal and

the temporal lobes.

Superior longitudinal fasciculus: It is the largest bundle that curves along the superior margin of insula connecting the frontal lobe to parietal, temporal and the occipital lobes. A part of it is parallel to the superior

occipitofrontal fasciculus and is separated from it by the corona radiata and the internal capsule.

Arcuate fasciculus – It connects the superior temporal gyrus to the perisylvian fronto-parietal cortex and is involved in language function.

Uncinate fasciculus: It curves around the sylvian fissure connecting inferior frontal lobe (orbital and frontopolar regions) with the superior temporal gyrus.

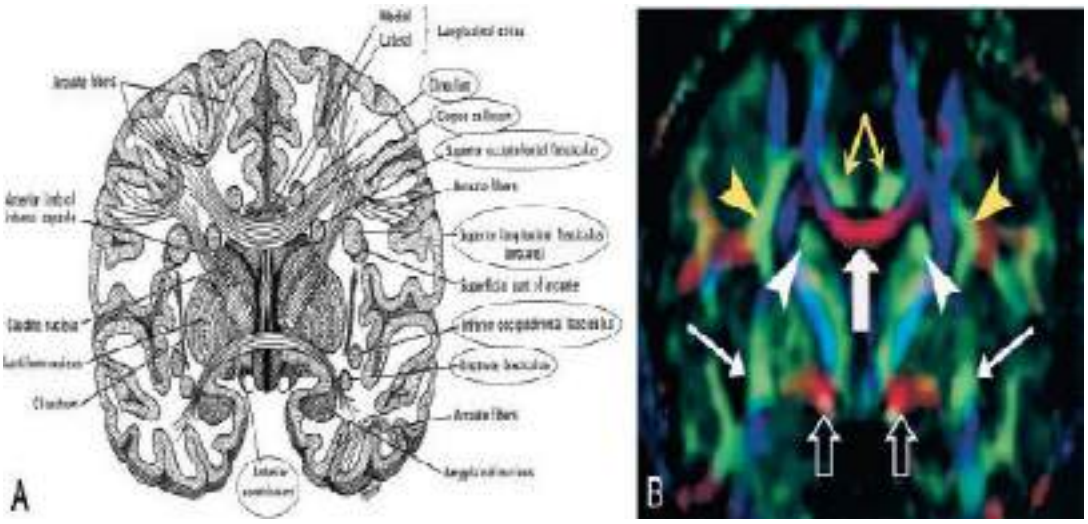


Figure 6: A & B Diagrammatic representation and colour coded coronal FA map showing uncinate fasciculus (white arrow), superior longitudinal fasciculus (yellow arrowhead), superior occipitofrontal fasciculus (white arrowhead).

Inferior longitudinal fasciculus (Occipito temporal fasciculus): It connects the
occipital and the temporal lobes.

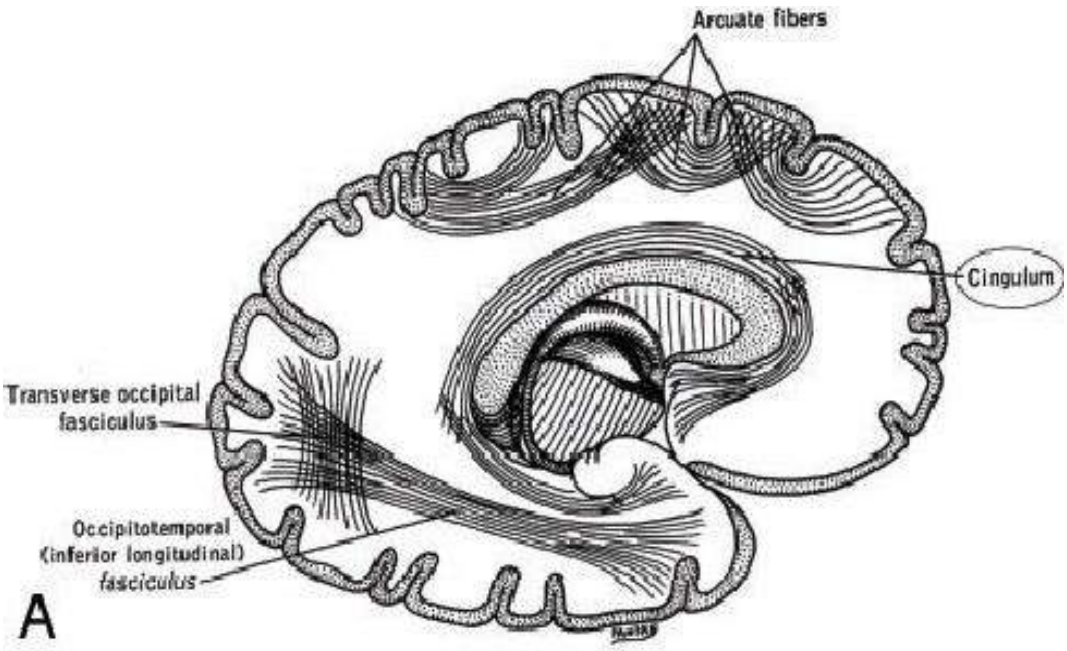


Figure 7: Diagrammatic representation showing inferior longitudinal fasciculus (white arrow)

Role of various imaging modalities in diagnosis of MTLE:

Imaging is pivotal in the evaluation and management of patients with seizure disorders. Numerous neuroimaging modalities [e.g., volumetric MRI, magnetic resonance spectroscopy (MRS), and positron emission tomography (PET)], have provided convincing data from MTLE patients with HS (TLE-HS) that the structural, functional, or metabolic abnormalities may extend beyond the seizure-onset zone, such as to the contralateral temporal or extratemporal areas[16].

EEG

The role of EEG in temporal lobe epilepsy (TLE) and epilepsy surgery was first described by Kennedy and Hill in 1958[33]. The typical epileptiform abnormality is the characteristic spike or sharp wave with negative polarity and is often followed by a slow wave. The anterior temporal spikes have maximum negativity over the temporal basal electrodes (F7, F8, T1, T2, and sphenoidal electrodes). About one-third of patients with MTLE have bitemporal independent spikes or sharp waves mostly during non-REM sleep[20]. Interictal EEG shows anterior or mid-temporal spikes/sharp ipsilaterally to the focus, in combination with non-epileptiform regional slowing. These changes may be bilateral but usually predominates ipsilaterally. Ictal EEG changes are marked by rhythmic temporal alpha or theta activity within 30seconds of clinical onset[29]. Williamson et al. reviewed interictal scalp EEG abnormalities in MTLE and reported 42% of patients to have bitemporal independent spikes or sharp wave[34]. Typical IED (Interictal Epileptiform Discharges) and/or intermittent slow waves in the anterior temporal region were present in 94% of patients. The strictly unilateral changes (observed in 52%) correlated with the side of the seizure origin in 94% of patients. The more lateralized the spikes, the more predictive they are for the side of the seizure onset[35]. Sometimes postictal changes could lateralise the seizure onset. Postictal EEG changes in TLE could be in the form of unilateral or bilateral slowing.

Lateralized postictal slow waves could be present in up to 70% of patients with MTLE[34].

CT

CT has the advantage of easy availability and a low operating cost. The success of CT in detecting lesions in focal epilepsies is low[36]. The lower sensitivity of CT is due to poor resolution of the temporal fossa due to which it is not useful in detecting mesial temporal lobe sclerosis[37].

MRI

Routine anatomic MRI has contributed immensely to identifying and characterizing culprit lesions such as Mesial Temporal Sclerosis, which constitute over 70% of cases of TLE. The morphological changes in mesial temporal lobe sclerosis can be grouped into primary and secondary. The primary changes include:

• A small atrophic unilateral hippocampus

• Hyperintensity on both T2 W and FLAIR images (Fluid attenuated inversion recovery images)

• Loss of the hippocampal internal architecture and that of normal digitations of the head.

• Previous studies documented that visual MRI evaluation of hippocampal size, architecture and signal intensity changes have sensitivities of 87-100% with the eye being able to detect asymmetry of 14% or more[38,39].

The secondary changes on the other hand include:

• Unilateral atrophy of the mamillary body, fornix columns (circuit of paper), and the amygdala.

• Increased T2 W signal in the anterior temporal lobe white matter with loss of grey-white demarcation in the ipsilateral anterior temporal lobe.

• Unilateral dilatation of the temporal horn (a less reliable secondary sign)

• Unilateral atrophy of the collateral white matter bundle.

These secondary changes are seen in about 40-60% of patients with MTS. The secondary changes alone are unreliable, but there is increased diagnostic accuracy when considered with the primary findings[40].

Conventional electrophysiological and neuroimaging techniques sometimes fail to infer the location and/or the extension of the epileptogenic zone (EZ)[41]. In this context, neuroimaging techniques such as diffusion tensor imaging (DTI) can provide further insight into the pathophysiology of MTLE-HS.

Diffusion Tensor Imaging: A brief description and physiological basis

Physics[14,42,43]:

Diffusion is a process of random motion of molecules called as Brownian motion[14]. It is thermally driven, the rate of diffusion given by the equation,

$$\langle r^2 \rangle = 6Dt$$

$\langle r^2 \rangle$ denotes the mean squared displacement of the molecules, t the diffusion time and D the diffusion constant. The diffusion constant is the average displacement of the molecule in the observed time. Higher values indicate more mobility.

In the clinical setting, ADC is measured which reflects in vivo diffusion that cannot be separated from active transport, changes in membrane permeability and movement along the pressure gradient.

Stejskal – Tanner Diffusion Encoding:

A pair of diffusion sensitising, equal and opposite motion probing gradients, are applied to a T2-weighted spin-echo sequence, before and after the 180-degree refocusing pulse. If there is molecular motion, there is change in phase position during the application of diffusion sensitising gradients, resulting in incomplete rephasing and signal loss. The diffusion contrast is given by the equation,

$$S_i = S_0 . e^{-b.ADCi}$$

Si is the signal intensity along the direction i.

S0 is the signal intensity without the diffusion gradient.

ADCi is the ADC in the direction i

b is given by the formula,

$$b = \gamma^2 G^2 \delta^2 (\Delta - \delta /3)$$

where γ is the gyromagnetic ratio

G is the amplitude of diffusion measured in millitesla per meter.

δ is the duration of diffusion gradient in milliseconds.

Δ is the interval between the onset of diffusion gradient before and after the rephasing pulse.

Units of b is seconds per square millimeter, ADC is millimeter square per second.

Raising b values increases the diffusion weighting.

ADC is the apparent diffusion coefficient given by the formula,

$$ADC_i = -\ln (Si/S_0)/b$$

ln is the natural logarithm.

Si is the signal intensity in a given voxel in direction i with a given b value.

S0 is the signal intensity in a given voxel without diffusion sensitizing gradients.

Isotropy and anisotropy:

The tendency of molecules to move equally in all directions is called isotropy. In brain, isotropic diffusion is seen in CSF spaces. In clinical range of b values, grey matter is considered to show isotropic diffusion. Here,the direction of diffusion sensitising gradient is considered unimportant because ADCi is same for all directions i.

In white matter, diffusion is strongly anisotropic, occurring maximally in the same direction as white matter tracts. Larger ADC values are seen in the direction parallel to the tracts compared to the orthogonal direction. It is a property of the integrity of myelin sheath and axonal membrane[1]. So, more than one direction is required to characterise anisotropic diffusion. To overcome this problem, rotationally invariant

measures like trace ADC and geometric mean DWI are used. It is derived from the DWIs in minimum of three directions S_1, S_2 and S_3

$$S_{DWI} = S_0 . e^{- b.ADC}$$

Where ADC = $(ADC_1 + ADC_2 + ADC_3)/3$.

ADC is the average of three ADCs along three orthogonal directions and is rotationally invariant. It is also known as the mean diffusivity, trace ADC or ADC.

ADC mapping in healthy brain and pathology:

In clinical range of b values, in healthy adult brain, there is little difference between grey and white matter. Mean diffusivity of grey matter is 0.67- 0.83 x $10^{-3}mm^2/s$ & 0.64 – 0.71 x $10^{-3}mm^2/s$ for white matter. In neonates, ADC is very high at term, dropping steeply in first 2 years, gradually reaching the normal values in adulthood, at varying rates in different parts of the brain. ADC values tend to increase again after the age of 40.

Abnormally reduced ADC values are seen in acute cerebral ischemia, conditions causing cytotoxic edema such as status epilepticus and hypoglycemia. Infectious etiologies also cause reduced ADC measurements like abscess, subdural, intradural or intraventricular empyema. Epidermoid tumors also have restricted water motion and bright signal on diffusion weighted images. Finally, highly cellular tumors, acute demyelination, metabolic disorders, toxic exposures also have reduced diffusion.

The diffusion tensor:

White matter tracts are highly anisotropic, and this property can be exploited for characterisation and anatomic mapping of these tracts. White matter is subjected to motion probing, diffusion sensitising gradients in atleast 6 non collinear directions, and with one b 0 image, a tensor is obtained. The tensor, 3 x 3 matrix of vectors is a mathematical model of 3D diffusion anisotropy.

The diffusion ellipsoid that describes the ADC of water molecules at a particular time, is defined by 6 variables in different directions. It is a sphere for isotropic diffusion, and ellipsoid for anisotropic diffusion. The elements of a tensor above the diagonal are same as that below the diagonal, termed as conjugate symmetry.

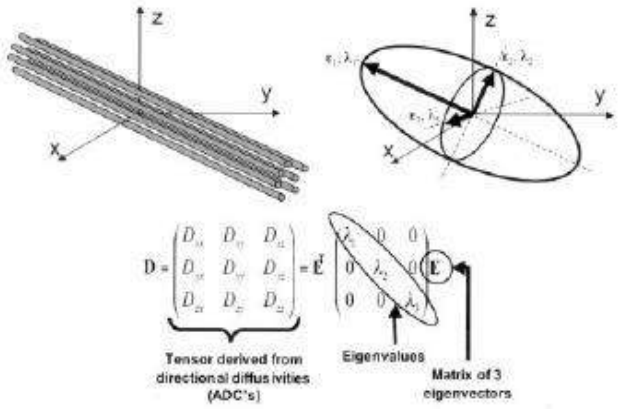


FIG 1. *Top left*, Fiber tracts have an arbitrary orientation with respect to scanner geometry (*x, y, z* axes) and impose directional dependence (anisotropy) on diffusion measurements.

Top right, The three-dimensional diffusivity is modeled as an ellipsoid whose orientation is characterized by three eigenvectors (ϵ_1, ϵ_2, ϵ_3) and whose shape is characterized three eigenvalues (λ_1, λ_2, λ_3). The eigenvectors represent the major, medium, and minor priniciple axes of the ellipsoid, and the eigenvalues represent the diffusivities in these three directions, respectively.

Bottom, This ellipsoid model is fitted to a set of at least six noncollinear diffusion measurements by solving a set of matrix equations involving the diffusivities (*ADC's*) and requiring a procedure known as matrix diagonalization. The major eigenvector (that eigenvector associated with the largest of the three eigenvalues) reflects the direction of maximum diffusivity, which, in turn, reflects the orientation of fiber tracts. Superscript *T* indicates the matrix transpose.

Diffusion tensor parameters:

By subjecting the tensor matrix to diagonalization, a set of three Eigen values representing major, medium and minor principle axes are obtained with their corresponding Eigen vectors. They describe the directions and lengths of the three diffusion ellipsoids axes. The largest vector is the primary Eigen vector, with its Eigen value $\lambda 1$, denotes the

magnitude and direction of the greatest water diffusion. It is also termed longitudinal diffusivity and used in fibre tractography indicating the orientation of axons. The second and third vectors, λ2 and λ3 are orthogonal to the primary vectors and their mean represents radial diffusivity**.**

Trace D is the sum of the three eigen values, D = λ1 + λ2 + λ3.

The mean diffusivity (MD) or apparent diffusion coefficient (ADC) is the mean of three eigen values and is given by the formula,

ADC = D_{av} =λ1 + λ2 + λ3 ÷ 3

Fractional anisotropy (FA):

FA is derived from the standard deviation of the three Eigen values and is given by the formula,

$$\mathrm{FA} = \sqrt{\frac{3}{2}} \frac{\sqrt{(\lambda_1 - \hat{\lambda})^2 + (\lambda_2 - \hat{\lambda})^2 + (\lambda_3 - \hat{\lambda})^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

λ1, λ2, λ3, are the three eigen values and λ is the mean value.

Fractional anisotropy FA ranges from 0 to 1[14].

Decreased anisotropy is a common feature of white matter tract disease. FA (fractional anisotropy) is often considered a measure of “white matter integrity” though changes in FA may be caused by many factors. Diffusion tensor imaging exploits this property of reduced anisotropy to recognise diseased neurons before they show up on conventional imaging. DTI holds potential as a useful tool for investigating deficits in the integrity of temporal and extratemporal white matter fiber tracts involved in MTLE[44].

Neuronal loss at the seizure focus in MTLE results in alteration of white matter tracts connecting the focus to other brain regions, which then may cause structural changes in remote but anatomically connected brain regions[45]. Disruption of the microstructural environment in the brain caused by various neurologic conditions, including intractable epileptic

disorders, will lead to changes in water diffusivity, even in structures without apparent abnormalities on conventional MRI[46]. In the white matter of the brain, diffusion anisotropy is primarily caused by cellular membranes, with some contribution from myelination and the packing of the axons. Anisotropic diffusion can indicate the underlying tissue orientation[47].

Role of Diffusion Tensor Imaging in Mesial Temporal Lobe Epilepsy - **Diffusion tensor imaging of Hippocampal formation in temporal lobe epilepsy:**

The hippocampus is an important structure in temporal lobe epilepsy, and hippocampal sclerosis is the etiology in nonlesional temporal lobe epilepsy. In addition to visual inspection of high resolution MR images taken orthogonal to hippocampal formation, quantification of hippocampal volume and T2 signal can increase the sensitivity of detection of hippocampal sclerosis. Assaf et al[48] in 2003 analyzed the mean diffusivity and fractional anisotropy of 12 patients with unilateral temporal lobe epilepsy and compared them with 14 healthy controls. They found significant increase in mean diffusivity and decreased fractional anisotropy in the Hippocampal formation of ipsilateral side compared to contralateral side in patients. Comparing with the controls, the mean diffusivity remained statistically higher but the fractional anisotropy did not reach significant differences, though they were lower.

In a study by Sarah Treit et al[49] in 2019, High-resolution DTI, T1, and quantitative T2 of hippocampus was acquired in 18 preoperative TLE patients and 19 healthy controls. High-resolution mean diffusion-weighted images enabled visualization of internal hippocampal architecture, used to visually identify HS with 86% specificity and 93% sensitivity. Mean diffusivity (MD) elevations were regionally heterogenous within the hippocampus and varied across TLE patients. The spatial location of diffusion abnormalities corresponded with the location of focal subfield neuron loss, gliosis, and reduced myelin staining abnormalities identified

with postsurgical histology in four subjects who underwent anterior temporal lobectomy. Whole-hippocampus MD and T2 relaxation times were higher, and fractional anisotropy (FA) and volumes were lower in TLE patients relative to controls. Left hippocampus MD correlated with verbal memory in the TLE group.

AMR OM AZAB et al[50] in 2018 conducted a study to demonstrate the role of DTI in diagnosis of temporal lobe epilepsy. This prospective study included 40 patients diagnosed clinically as having TLE and twenty control subjects. The patients and control groups are examined by conventional magnetic resonance imaging (MRI) followed by DTI and tractography. EEG examination, was performed to 36 patients only, and 4 were missed during followup. It was done to support the clinical diagnosis of TLE and to help in the lateralization of the site of seizure focus to be compared with DTI results. The calculated cut off value regarding fractional anisotropy (FA) difference between both hippocampi was 0.014. 28 patients with FA differences above this value were considered as DTI positive of hippocampal abnormality and 12 patients were below this value and were considered as DTI negative. FA differences between both hippocampi in patients' group were significantly increased as compared with the control group. The study concluded that DTI can detect hippocampal abnormalities even in patients with normal conventional MR, so it can be used to lateralize seizure side, thus increase the diagnostic accuracy before epilepsy surgery.

Diffusion tensor imaging fimbria- fornix (Limbic) in temporal lobe epilepsy patients:

Fimbria – fornix is a major afferent- efferent pathway of the hippocampus. Concha L et al[51] in 2009 observed strikingly symmetrical bilateral abnormalities of axonal integrity in the fornix and cingulum in a series of patients with unilateral mesial temporal sclerosis. Their findings suggest that TLE with unilateral mesial temporal sclerosis is associated with bilateral limbic system pathology. Concha L et al[52] in 2010 studied the

histopathology of fimbria - fornix in 11 medically intractable temporal lobe epilepsy patients with and without mesial temporal sclerosis. They found strong positive correlation between the fractional anisotropy of fimbria – fornix with cumulative axonal membrane circumference and axonal density. The myelin thickness was negatively correlated. The changes were bilateral suggesting etiology other than degeneration alone. Their study provides a strong validation for DTI as a measure of white matter pathology.

The cingulum and fornix are integral components of the limbic circuit that mediate the expression of epileptogenicity arising from mesial temporal structures. The TLE-induced alteration makes them suitable candidates as biomarkers of laterality. Interhemispheric variation of FA in the posteroinferior cingulum and crus of the fornix have lateralized MTLE in individual cases[44]. The related microstructural changes can be detected using segmentation or fiber tracking (FT) with DTI data. Most previous studies have reported bilateral alterations of fractional anisotropy (FA) and mean diffusivity (MD), as indices of fiber integrity and overall diffusivity, respectively as a way to differentiate the DTI-based structural changes in subjects with unilateral MTLE from those in nonepileptic controls[44].

Thalamus in temporal lobe epilepsy:

Thalamus has strong anatomic connection with medial temporal area and plays a role in seizure modulation. Kim C H et al[53] in 2010 studied 9 patients with hippocampal sclerosis and 9 patients with cortical dysplasia in temporal lobe neocortex. All of them underwent surgery with good seizure outcome and the pathologic diagnosis was proved in all cases. ROI was placed in centre of bilateral thalami. The MD was increased in bilateral thalami in all patients compared to controls while the FA did not differ. Ipsilateral MD was higher in mesial temporal sclerosis cases compared to patients without hippocampal sclerosis.

C. Chen et al[54] in 2019 consecutively recruited 51 unilateral TLE-HS patients (26 with and 25 without sGTCS) and 22 healthy controls.

After correction, the sGTCS group showed lower FA than the non-sGTCS group (P = 0.03), and lower FA as well as higher MD than controls in the ipsilateral probabilistic hippocampal-thalamic pathway (pHTP). The non-sGTCS group only showed higher corrected MD in the ipsilateral pHTP relative to controls. Corrected FA or MD in the contralateral pHTP did not differ among groups. The thalamic subregion connected to the hippocampus (TSCH) was located in the mesial aspect of the thalamus, and it was atrophied in the sGTCS group compared to the non-sGTCS group and controls. They concluded that sGTCS was associated with impaired integrity of the pHTP as well as structural and functional abnormalities in the medial thalamus. The medial thalamus is important in seizure generalization in mTLE.

Extratemporal white matter in temporal lobe epilepsy:

Yu-Hsuan A Chang et al[55] in 2019 evaluated DTI, volumetric MRI (vMRI), and resting-state functional MRI (rs-fMRI) in 46 patients with TLE and 33 healthy controls. Patients with left TLE and right TLE both demonstrated pronounced microstructural alterations (ie, decreased FA and increased MD) spanning the entire frontal and temporo-limbic superficial white matter (SWM), which were highly lateralized to the ipsilateral hemisphere. Conversely, reductions in cortical thickness in vMRI and alterations in the magnitude of the rs-fMRI response were less pronounced and less lateralized than the microstructural changes. FA and MD within SWM in left medial temporal lobe/posterior cingulate (LMT/PC) regions were the most robust predictors of verbal memory, and that these associations were independent of left hippocampal volume. These findings suggest that microstructural loss within the SWM is pronounced in patients with TLE, and injury to the SWM within the LMT/PC region plays a critical role in verbal memory impairment.

Lin JJ et al[56] investigated the integrity of two major frontal-temporal white matter association tracts, uncinate fasciculus (UF) and arcuate fasciculus (AF), and their clinical correlates in TLE. Fractional anisotropy

(FA) and apparent diffusion coefficient (ADC) of UF and AF ipsilateral to the side of seizure onset were abnormal when compared to healthy controls. Furthermore, lower UF FA correlated with earlier age of seizure onset. This suggests that frontal-temporal white matter tracts are vulnerable to recurrent seizures and/or the factors precipitating the epilepsy[56]. There have been several studies demonstrating correlations between white matter DTI findings and duration of epilepsy. Govindan et al found that diffusion abnormalities associated with duration of epilepsy suggest progressive changes in ipsilateral uncinate and arcuate fasciculus due to chronic seizure activity.[38]

Cognition in temporal lobe epilepsy:

Riley et al[58] in 2010 studied the integrity of white matter tracts and its impact on the cognitive function in 12 TLE patients. They found white matter abnormalities in fornix, uncinate and arcuate fasciculus, inferior longitudinal fasciculus, motor projection fibres and the cerebellum. These abnormalities correlated with the cognitive performance. Alteration in the splenium of corpus callosum correlated with the age of onset.

Uncinate fasciculus connects temporal lobe with inferior frontal gyrus. Abnormalities in the uncinate fasciculus have been shown to be associated with social anxiety and depression. Preferential pathway for seizure spread is the fornix, stria terminalis, amygdala fugal fibres and the uncinate fasciculus. A study in 2008 by Diehl et al[59] with 28 patients of TLE showed increased ADC and reduced fractional anisotropy in UF affected immediate and delayed auditory and visual memory.

Shaimaa H Soliman et al[60] in 2018 studied the utility of DTI in exploration of white matter microstructure changes and clarify their relation to episodic memory in TLE. DTI was performed on 30 (18 left, 12 right) TLE patients and 20 healthy controls. FA and MD were calculated for 6 fiber tracts; parahippocampal cingulum (PHC), superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), fornix (FORX), uncinate fasciculus (UF) and corpus callosum (CC). All TLE patients had

episodic memory impairment. In left TLE patients, there was significant correlation between DTI parameters of left (PHC, SLF, UF, FORX) and verbal memory. Whereas, in right TLE patient, significant correlation between DTI parameters of right ILF and visual memory. The study concluded that TLE patients had multiple micro-structural WM tracts abnormalities and episodic memory impairment. Both are structurally and functionally related.

MATERIAL AND METHODS

SOURCE OF DATA

Patients with a clinical picture of temporal lobe epilepsy, referred to our department (opd/epilepsy clinic) and with EEG features of temporal lobe epilepsy undergoing MRI examination of brain.

We initially planned to study DTI changes in TLE patients as 2 separate categories, where one category consists of hippocampal sclerosis in MRI and the other category has normal MRI. However, in view of the pandemic, we were able to recruit only two TLE patients who had normal MRI. So, we combined both categories of patients and compared them with normal controls.

INCLUSION CRITERIA

Both males and females,

(i) with clinical features and EEG consistent with temporal lobe epilepsy, with or without hippocampal sclerosis in 3Tesla MRI

(ii) normal healthy controls (age matched) with no neurologic deficit and normal MRI imaging.

EXCLUSION CRITERIA:

1. Presence of intraaxial structural abnormalities in locations other than temporal lobe, as it might interfere with the diffusion tensor imaging values.

METHOD OF COLLECTION OF DATA

This is a Prospective- Observational (case - control study) study.

All patients underwent conventional MRI, temporal lobe protocol and diffusion tensor imaging. All of them were seizure free for more than a week at the time of imaging. The control group underwent conventional MRI and diffusion tensor imaging. Whole-brain Diffusion Tensor Imaging (DTI) will be acquired using Echo Planar Imaging.

We use Diffusion Tensor Imaging (DTI) and Statistical Parametric Mapping (SPM) to calculate rotationally invariant anisotropy and diffusivity maps and study objectively tissue organization in the 3 groups.

OUTCOME

Outcomes will be studied in the form of fractional anisotropy and mean diffusivity differences in the involvement of white matter tracts within and beyond hippocampus and will be compared between patient and control groups.

STATISTICAL ANALYSIS

All the continuous variables will be tested for the normality using Shapiro Wilk's test. Variables were normally distributed and expressed as mean ±SD. Categorical variables will be expressed either as percentage or proportion.

- Comparison of categorical variables (age) will be done by Chi -square test or Fisher's exact test based on the number of observations.
- Comparison of normally distributed continuous variables between cases and controls will be done by independent sample T test.
- Comparison of right and left sided variables within controls will be done by paired T test.
- All the P values less than 0.05 were considered statistically significant.
- Data entry will be done in MS excel worksheet.
- Data analysis will be done by SPSS software version 16.0

Imaging protocol:

The examinations were performed in 3T SIEMENS, MEGNETOM MRI system, using the head coil. Our conventional imaging protocol consists of T1W sequence in the sagittal plane, T2W in the axial plane and FLAIR in the coronal plane.

Parameters for conventional imaging

	T1W sagittal	T2W axial	FLAIR coronal
TR	429 ms	3000 ms	11000 ms
TE	12 ms	80 ms	100 ms
TI			2800 ms
Matrix	320 x 256 mm	420 x270 mm	244 x 152
Slice thickness	4 mm	4 mm	5mm
Slice gap	1 mm	1 mm	1 mm

Temporal lobe protocol for epilepsy consists of 3 mm oblique coronal
sections orthogonal to hippocampus in T2W, T1 inversion recovery and FLAIR
sequences.

Parameters for temporal lobe protocol

	T2W	T1W IR	T2WFLAIR
TR	3746 ms	1400 ms	11000 ms
TI		400 ms	2800 ms
TE	85 ms	15 ms	120 ms
Matrix	400 x 213 mm	316 x 199	336 x 210
Slice thickness	3 mm	3 mm	3 mm
Slice gap	Nil	Nil	Nil

DTI images were acquired in the axial plane using spin echo – echo planar imaging sequence using the following parameters.

TR	3500ms
TE	83 ms
FOV	224 mm
Matrix size	90 x 128 mm
Slice thickness	2.5 mm
B value	800

Diffusion sensitive gradients are applied in 30 directions. Duration of DTI sequence is 20 minutes 16 seconds.

T1W 3D TFE imaging was done with the following parameters for superimposing over the colour coded FA maps.

TR	8.4 ms
TE	4.1 ms
Matrix	256 x 256 mm
TFE factor	131
No of slices	145

Imaging is performed after a minimum of 7 days after the ictus as ADC values are known to alter in the peri ictal period.

Imaging analysis:

All DTI images were transferred to a workstation where image reconstruction and post processing analysis was performed using MATLAB and SPM software. Using probabilistic diffusion tensor atlas ROIs were placed in FA map superimposed over isotropic T1W images over bilateral hippocampi, body of fornix, para hippocampal gyrus, external capsule, thalamus, head of caudate nucleus, anterior and posterior cingulate gyrus, optic radiation, uncinate fasciculus, arcuate fasciculus, superior longitudinal fasciculus, inferior longitudinal fasciculus,

inferior fronto occipital fasciculus. FA and ADC values from each of these ROI was recorded

Observations & Results

Our study consisted of 16 cases with temporal lobe epilepsy (TLE) and 14 healthy controls. Mean age of cases was 29 years (±9 years) and mean age of controls is 33(±9 years) years. Although control group age was higher than cases, there was no significant statistical difference between mean ages of both groups (p=0.17).

Table 1: comparison of mean age of cases with controls

	Cases		Control		T	p-value
	Mean	SD	Mean	SD		
Age	28.69	8.87	33.29	9.31	-1.384	0.177

Figure 8: comparison of mean age of cases with controls.

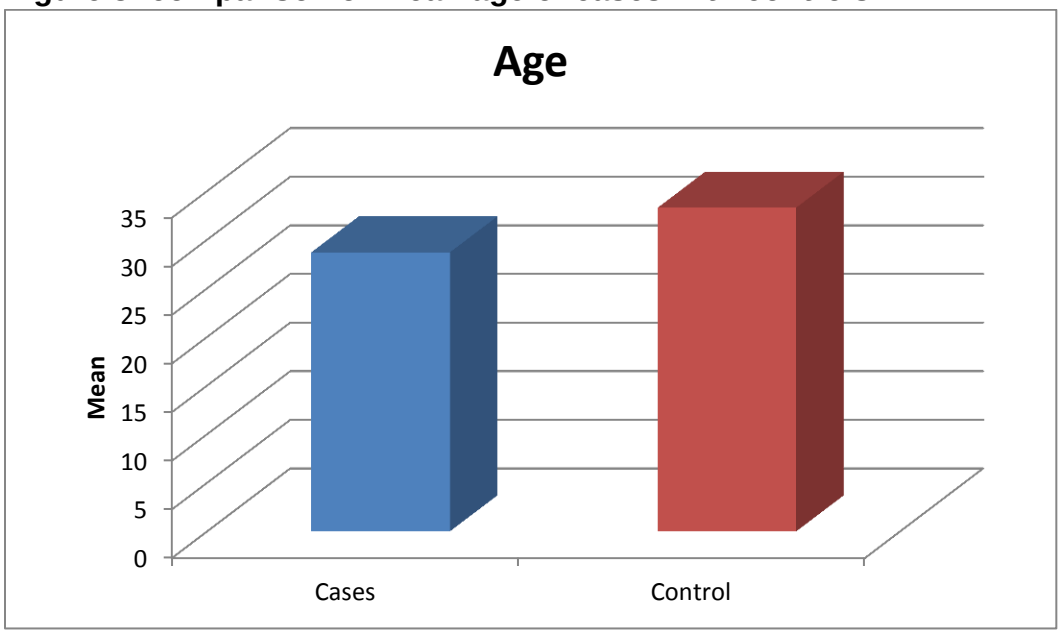
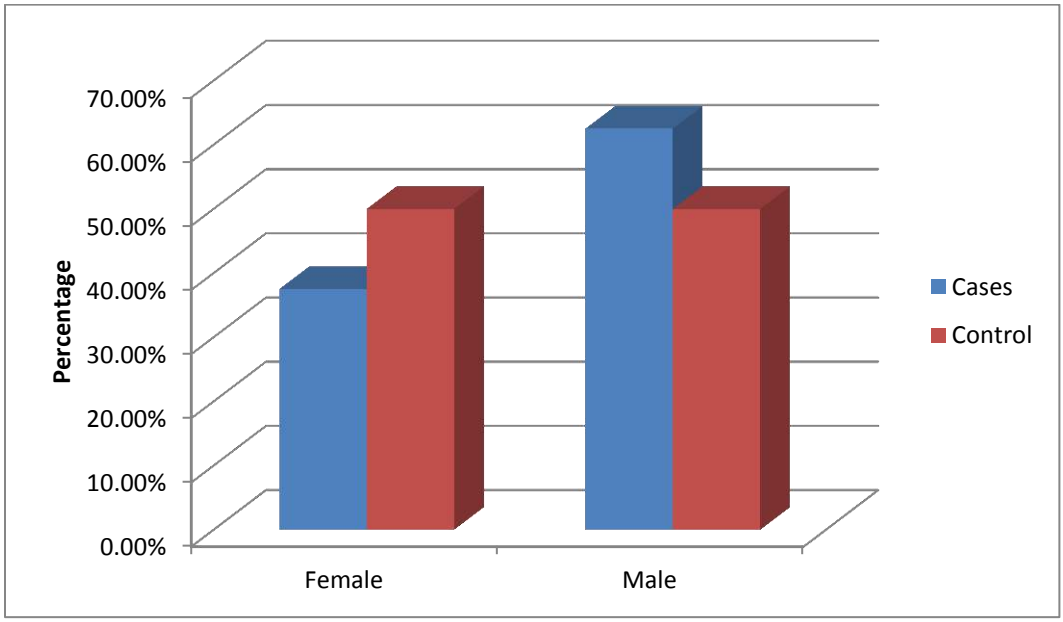


Table 2: comparison of gender distribution between cases and controls.

		Group				Total	Chi-square value	p-value
		Cases		Control				
Sex	Female	6	37.0%	7	50.0%	13	0.475	0.491
	Male	10	63.0%	7	50.0%	17		
Total		16	100.0%	14	100.0%	30		

Among cases, majority (63.0%) were males (n=10) and 37.0% were females (n=6), whereas in control group males(n=7) and females (n=7) constituted 50% each. There was no significant difference in gender distribution between cases and controls (p=0.49).

Figure 9: comparison of gender distribution between cases and controls.



Comparison of mean fractional anisotropy (FA) and mean diffusivity i.e., apparent diffusion coefficient (ADC) values between patients and controls: The diffusion tensor metrics derived from all region of interest and statistical results listed in following tables.

Table 3: comparison of hippocampus FA between patients and controls

Site	Cases		Control		T	p-value	Difference		95% CI of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
Hippocampus FA-C/L	0.178	0.016	0.171	0.019	0.954	0.348	0.01	0.01	-0.01	0.02
Hippocampus FA-I/L	0.154	0.013	0.163	0.016	-1.573	0.127	-0.01	0.01	-0.02	0.00
Hippocampus FA-Diff	0.023	0.006	0.009	0.007	6.301	0.000	0.01	0.00	0.01	0.02
95 % CI (lower to upper)	(0.020 to 0.026)		(0.005 to 0.012)							

In hippocampus, among patients FA was decreased ipsilateral to the side of TLE compared to contralateral side FA. When compared to controls, the mean of side-to-side difference of FA values is significantly higher in patients with the ipsilateral FA being less than contralateral side. Also, ipsilateral FA of cases is less compared to controls FA, but the difference fell just short of significance(p=0.12). However, FA of contralateral hippocampus in cases is more when compared to controls and doesnot show statistical significance which indicates altered FA values more on ipsilateral hippocampus of patients.

Figure 10: comparison of hippocampus FA between patients and controls

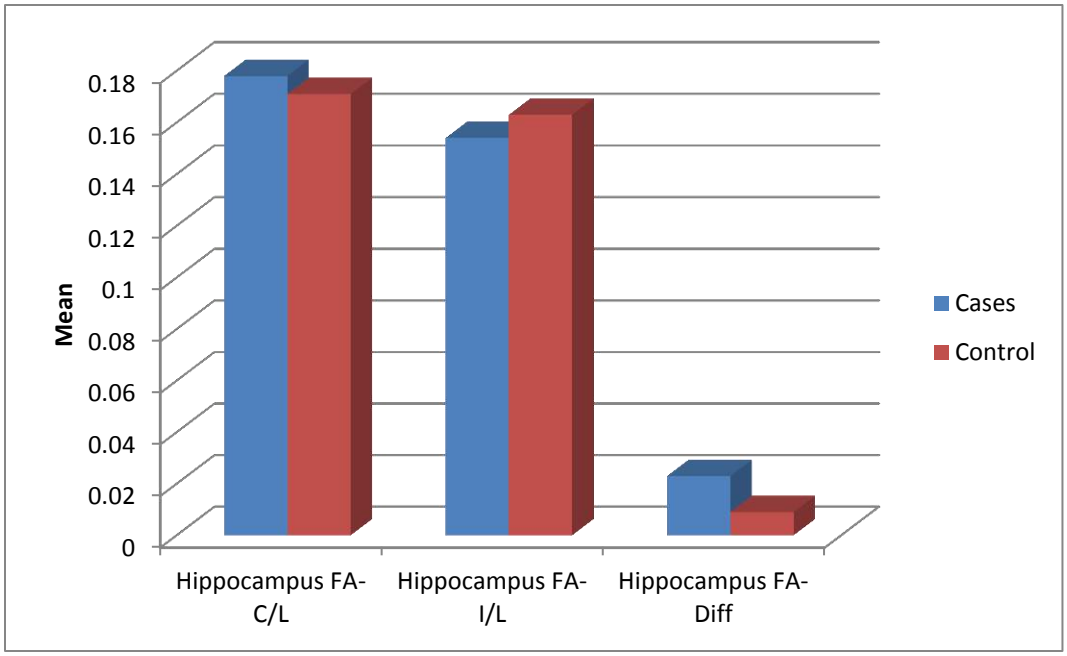


Table 4: comparison of hippocampus ADC between patients and controls

Site	Cases		Control		T	p-value	Difference		95% CI of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
Hippocampus ADC- I/L	1.224	0.155	1.120	0.097	2.161	**0.039**	0.10	0.05	0.01	0.20
Hippocampus ADC C/L	1.083	0.102	1.071	0.080	0.347	0.731	0.01	0.03	-0.06	0.08
Hippocampus ADC-Diff	0.141	0.107	0.049	0.039	3.050	**0.005**	0.09	0.03	0.03	0.15
95% CI (lower to upper)	(0.084 to 0.198)		(0.027 to 0.072)							

In hippocampus, among patient group ipsilateral ADC was higher compared to contralateral side. When compared to controls, the mean of side-to-side difference of ADC values was significantly higher in cases. The mean of ipsilateral ADC values of cases is significantly higher when compared to controls. However, the mean ADC of contralateral side in patients did not show statistically significant difference when compared to controls. This shows that DTI values are altered in ipsilateral hippocampus of patients significantly

Figure 11: comparison of hippocampus ADC between patients and controls

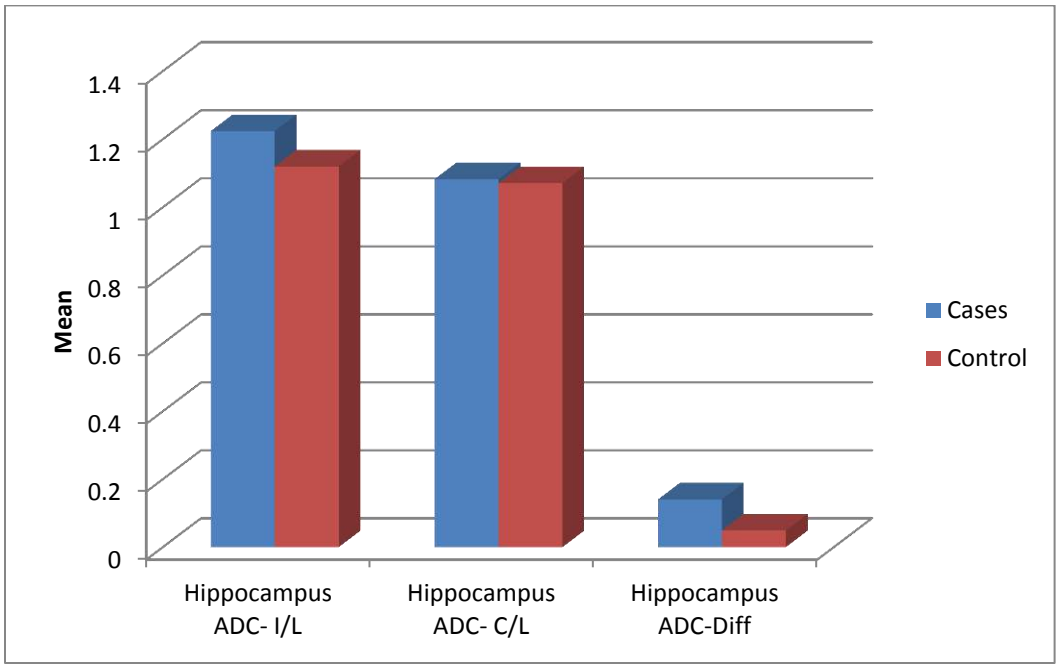


Table 5: comparison of parahippocampal gyrus FA between patients and controls

Site	Cases		Control		T	p-value	Difference		95% CI of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
PHG FA-C/L	0.163	0.021	0.169	0.013	-0.948	0.351	-0.01	0.01	-0.02	0.01
PHG FA-I/L	0.143	0.017	0.161	0.012	-3.170	**0.004**	-0.02	0.01	-0.03	-0.01
PHG FA-Diff	0.020	0.008	0.009	0.005	4.462	**0.000**	0.01	0.00	0.01	0.02
95% CI (lower to upper)	(0.016 to 0.024)		(0.005 to 0.012)							

In parahippocampal gyrus, among patients, ipsilateral FA was less than contralateral side. When compared to controls, the mean of side-to-side difference of FA values is significantly higher in cases compared to controls. Also mean of ipsilateral FA values of cases is significantly reduced compared to controls. However, contralateral mean FA of patients did not show statistically significant difference compared to controls although it is higher compared to controls. This shows that FA is altered in ipsilateral PHG of patients.

Figure 12: comparison of parahippocampal gyrus FA between patients and controls

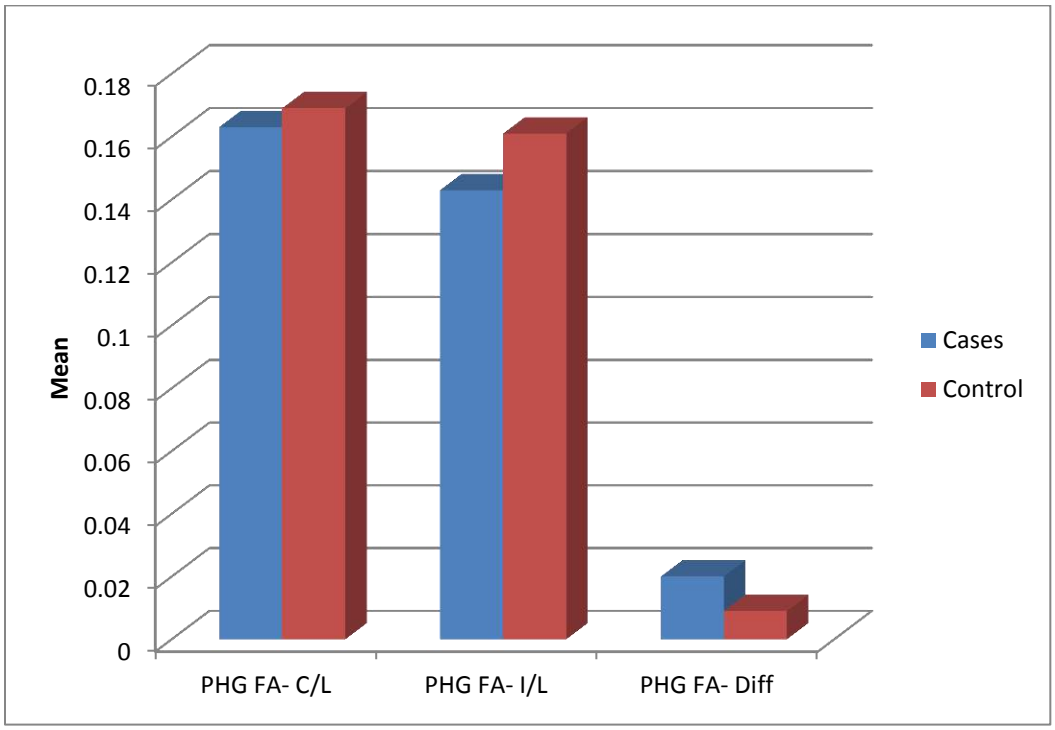


Table 6: comparison of parahippocampal gyrus ADC between patients and controls

Site	Cases		Control		t	p-value	Difference		95% CI of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
PHG ADC- I/L	1.439	0.138	1.309	0.098	2.949	**0.006**	0.13	0.04	0.04	0.22
PHG ADC- C/L	1.303	0.180	1.243	0.105	1.101	0.280	0.06	0.05	-0.05	0.17
PHG ADC-DIFF	0.136	0.095	0.066	0.039	2.600	**0.015**	0.07	0.03	0.01	0.13
95% CI (lower to upper)	(0.086 to 0.187)		(0.043 to 0.088)							

In parahippocampal gyrus, among patients the mean ADC of ipsilateral side was higher than their contralateral side. When compared to controls, the mean of side-to-side difference of ADC values was significantly higher in cases compared to controls. The mean of ipsilateral ADC values of cases was significantly higher than controls. But the contralateral mean ADC of cases did not show statistical significance compared to controls although the mean values was higher. This shows altered ADC in ipsilateral PHG of patients.

Figure 13: Comparison of parahippocampal gyrus ADC between patients and controls

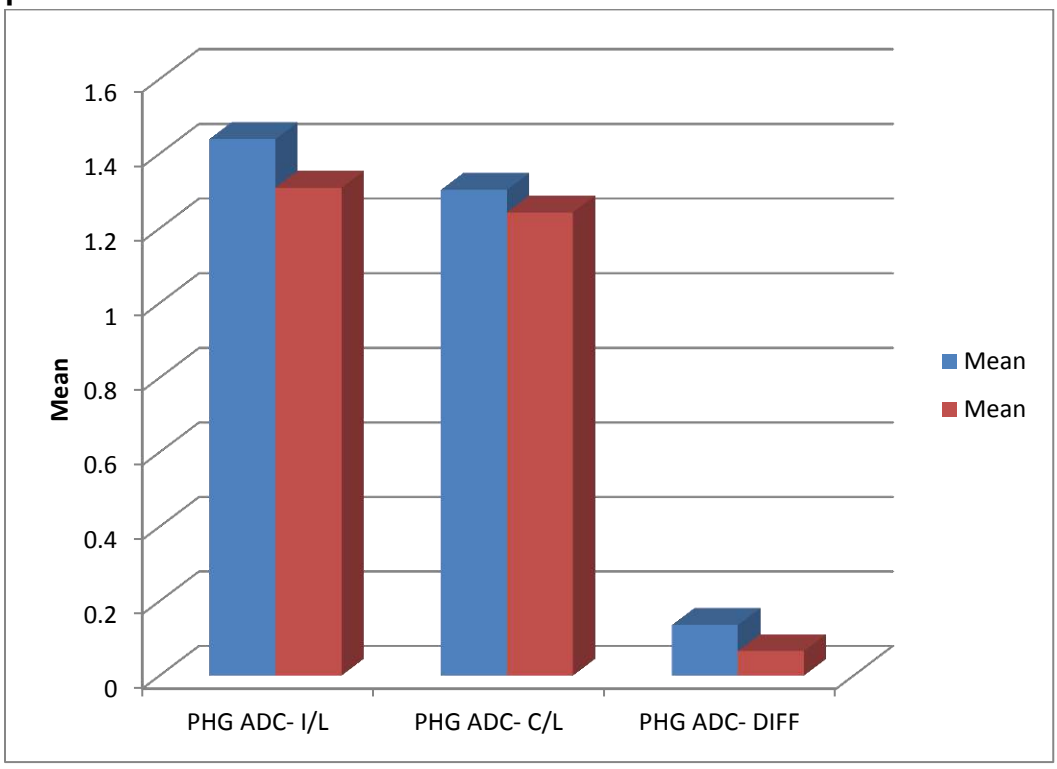


Table 7: comparison of caudate nucleus FA between patients and controls

Site	Cases		Control		t	p-value	Difference		95% CI of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
Caudate FA-C/L	0.151	0.026	0.168	0.015	-2.074	0.047	-0.02	0.01	-0.03	0.00
Caudate FA- I/L	0.152	0.022	0.161	0.016	-1.245	0.223	-0.01	0.01	-0.02	0.01
Caudate FA-Diff	-0.001	0.018	0.007	0.006	-1.531	0.137	-0.01	0.01	-0.02	0.00
95% CI (lower to upper)	(-0.010 to 0.009)		(0.004 to 0.011)							

In caudate, among patient group, mean FA of contralateral side was less than ipsilateral side but not significantly. When compared to controls, the mean of side-to-side difference of FA values did not differ significantly between both groups. Also mean of ipsilateral FA values of cases did not show significant difference compared to controls. However, contralateral mean FA of patients was less than controls and showed statistically significant difference.

Figure 14: comparison of caudate nucleus FA between patients and controls

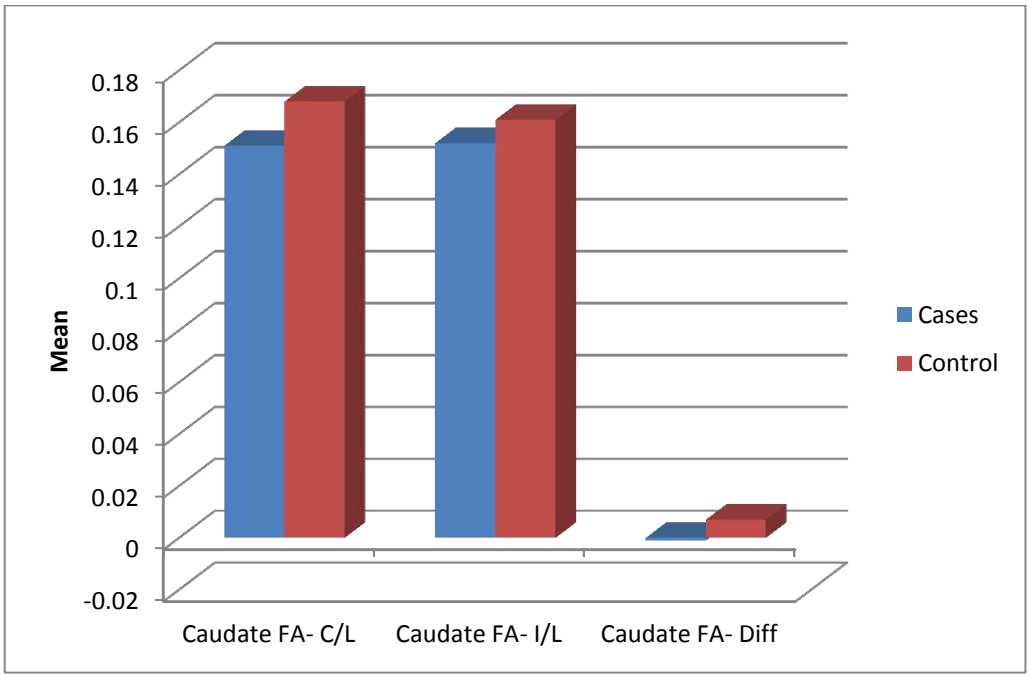


Table 8: comparison of caudate nucleus ADC between patients and controls

Site	Cases		Control		T	p-value	Difference		95% CI of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
Caudate ADC- I/L	1.070	0.306	1.057	0.221	0.130	0.897	0.01	0.10	-0.19	0.22
Caudate ADC- C/L	1.056	0.291	1.036	0.217	0.203	0.841	0.02	0.09	-0.17	0.21
Caudate ADC-Diff	0.014	0.071	0.021	0.011	-0.331	0.743	-0.01	0.02	-0.05	0.03
95% CI (lower to upper)	(-0.023 to 0.052)		(0.014 to 0.027)							

In caudate, among patient group ipsilateral mean ADC was higher than contralateral side but not significantly. When compared to controls, the mean of side-to-side difference of ADC values of patients was less and did not show statistically significant difference. Neither the ipsilateral nor the contralateral ADC of patients showed any statistically significant difference compared to controls.

Figure 15: comparison of caudate nucleus ADC between patients and controls

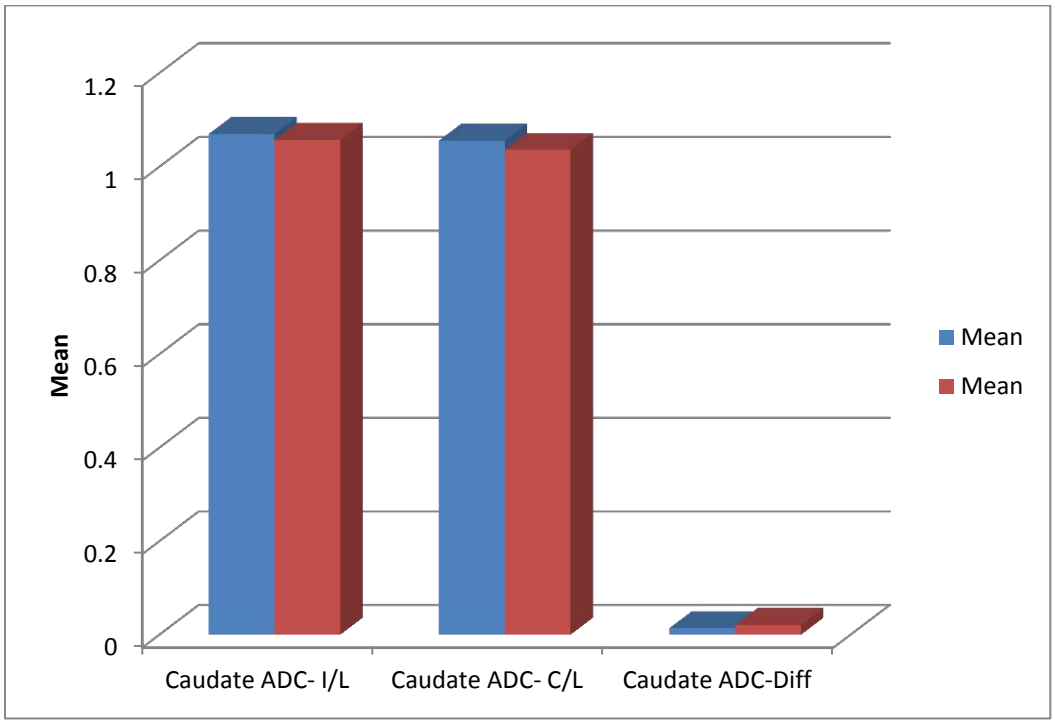


Table 9: comparison of thalamus FA between patients and controls

Site	Cases		Control		t	p-value	Difference		95% CI of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
Thalamus FA-C/L	0.288	0.018	0.297	0.021	-1.283	0.210	-0.01	0.01	-0.02	0.01
Thalamus FA-I/L	0.271	0.019	0.289	0.023	-2.444	**0.021**	-0.02	0.01	-0.03	0.00
Thalamus FA-diff	0.018	0.011	0.008	0.008	2.769	**0.010**	0.01	0.00	0.00	0.02
95% CI (lower to upper)	(0.012 to 0.023)		(0.003 to 0.012)							

In thalamus, among patient group, mean FA of ipsilateral side was significantly less than contralateral side. When compared to controls, mean of side-to-side difference of FA values was significantly higher in cases. The ipsilateral mean FA of cases was significantly reduced compared to controls. But the contralateral mean FA of patients did not differ significantly from controls although mean values was reduced. This indicates decreased FA of thalamus bilaterally with ipsilateral side showing statistical significance in patients.

Figure 16: comparison of thalamus FA between patients and controls

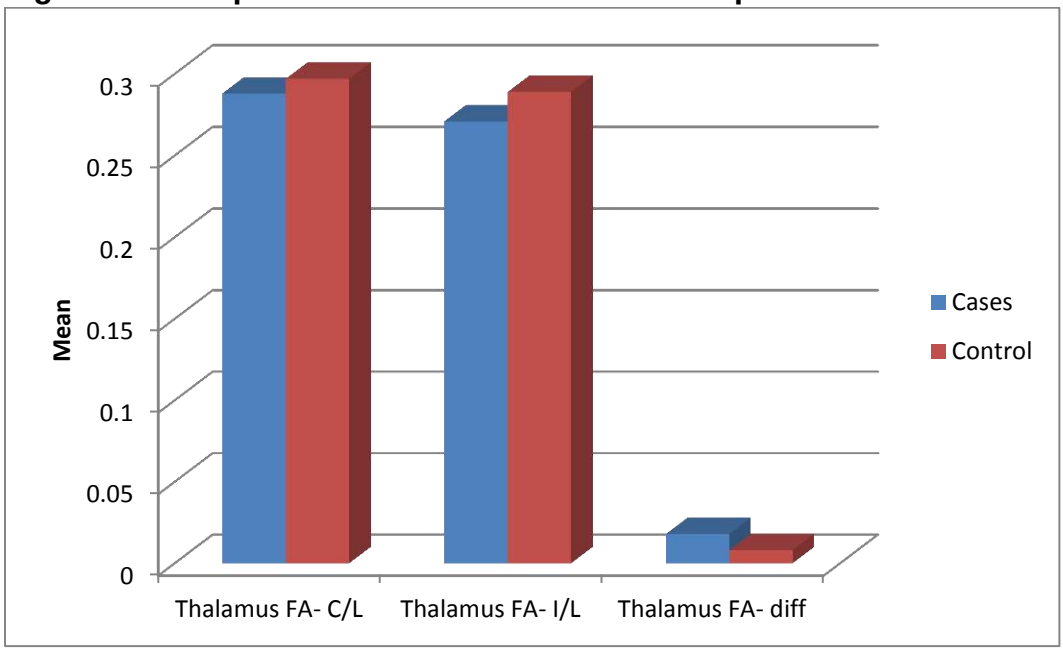


Table 10: comparison of thalamus ADC between patients and controls

Site	Cases		Control		t	p-value	Difference		95% CI of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
Thalamus ADC- I/L	1.055	0.106	1.031	0.120	0.571	0.573	0.02	0.04	-0.06	0.11
Thalamus ADC- C/L	1.010	0.101	1.009	0.117	0.036	0.972	0.00	0.04	-0.08	0.08
Thalamus ADC- Diff	0.045	0.043	0.023	0.022	1.734	0.094	0.02	0.01	0.00	0.05
95% CI (lower to upper)	(0.022 to 0.068)		(0.010 to 0.036)							

In thalamus, among patients group ipsilateral mean ADC was higher compared to the contralateral side. When compared to controls, the mean of side-to-side difference of ADC values of cases was higher and showed trend towards significance although it did not reach statistical difference. Neither the ipsilateral ADC nor the contralateral ADC of patients showed statistically significant difference compared to controls although the mean values of ADC was high in patients on both side compared to controls.

Figure 17: comparison of thalamus ADC between patients and controls

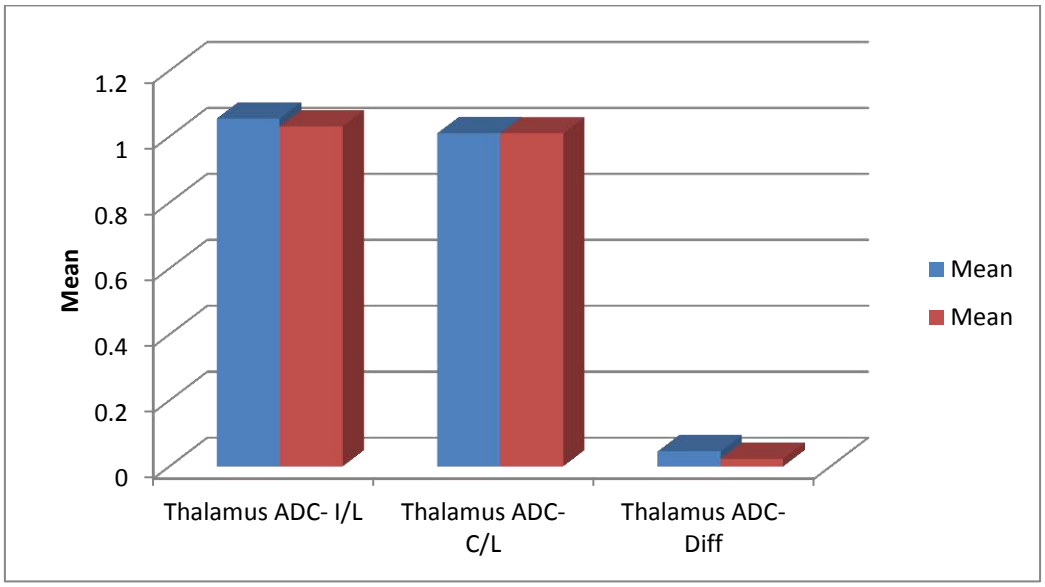


Table 11: comparison of external capsule FA between patients and controls

Site	Cases		Control		t	p-value	Difference		95% CI of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
External capsule FA-C/L	0.299	0.036	0.304	0.033	-0.436	0.666	-0.01	0.01	-0.03	0.02
External capsule FA-I/L	0.262	0.027	0.292	0.031	-2.856	**0.008**	-0.03	0.01	-0.05	-0.01
External capsule FA-Diff	0.037	0.027	0.012	0.007	3.352	**0.002**	0.03	0.01	0.01	0.04
95% CI (lower to upper)	(0.023 to 0.051)		(0.008 to 0.016)							

In external capsule, among patient group, mean FA of ipsilateral side was significantly less than contralateral side. The mean of side-to-side difference of FA values was significantly higher in cases compared to controls. The ipsilateral mean FA of cases was significantly reduced compared to controls. However, the contralateral mean FA of patients although less than controls, did not show statistical significance. This shows that external capsule FA of ipsilateral side in patients is altered significantly.

Figure 18: comparison of external capsule FA between patients and controls

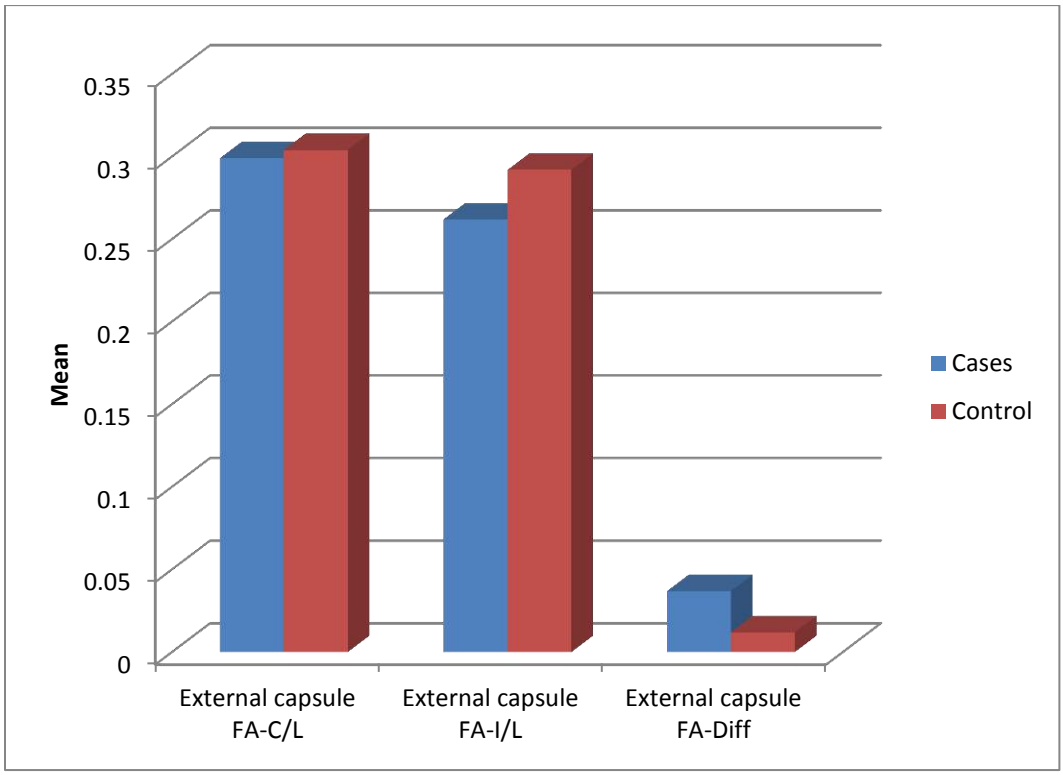


Table 12: comparison of external capsule ADC between patients and controls

Site	Cases		Control		t	p-value	Difference		95% CI of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
EC ADC-I/L	1.009	0.090	0.935	0.055	2.680	**0.012**	0.07	0.03	0.02	0.13
EC ADC-C/L	0.954	0.078	0.909	0.048	1.871	0.072	0.05	0.02	-0.00	0.10
EC ADC-Diff	0.056	0.040	0.026	0.014	2.593	**0.015**	0.03	0.01	0.01	0.05
95% CI (lower to upper)	(0.034 to 0.077)		(0.018 to 0.034)							

In external capsule, among patients group ipsilateral mean ADC was higher compared to the contralateral side significantly. Also the mean of side-to-side difference of ADC values of cases was higher compared to controls. The ipsilateral ADC of patients was significantly increased compared to controls. The contralateral ADC of patients was higher than controls ADC and showed a trend towards significance although it fell just short of statistical significance (p=0.07).

Figure 19: comparison of external capsule ADC between patients and controls

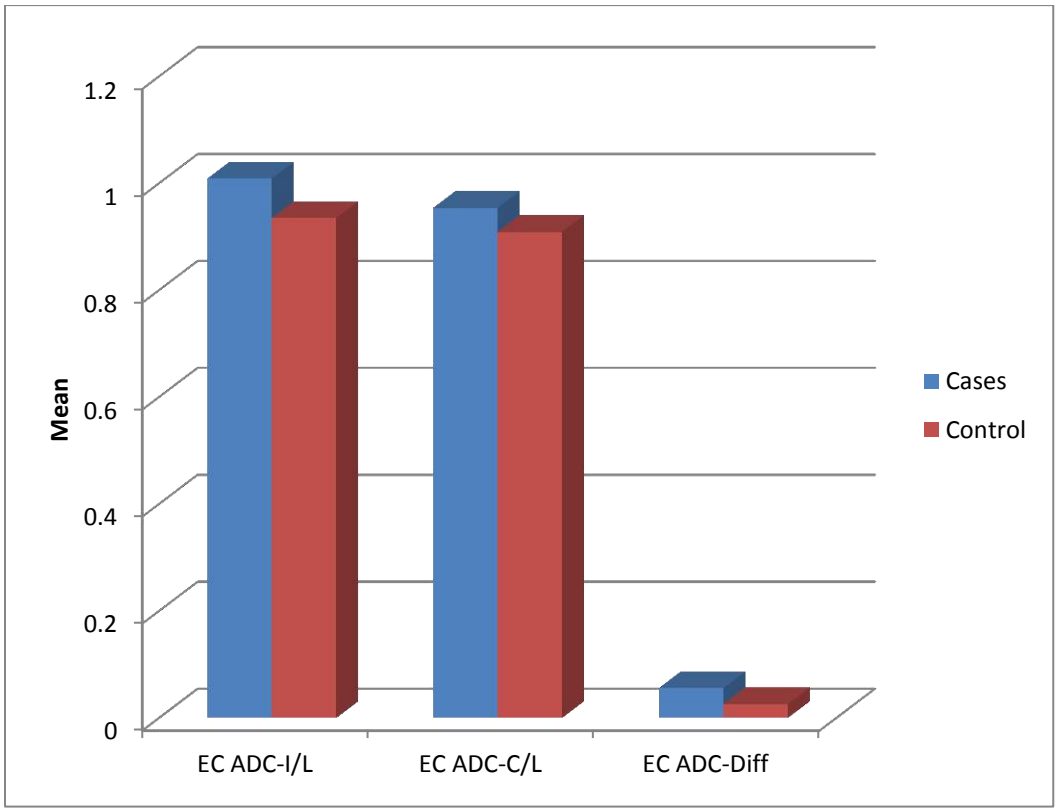


Table 13: comparison of anterior cingulate gyrus FA between patients and controls

Site	Cases		Control		t	p-value	Difference		95% CI of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
ACG FA- C/L	0.131	0.014	0.136	0.010	-1.292	0.207	-0.01	0.00	-0.02	0.00
ACG FA- I/L	0.126	0.016	0.132	0.011	-1.138	0.265	-0.01	0.01	-0.02	0.00
ACG FA- Diff	0.004	0.016	0.004	0.006	0.019	0.985	0.00	0.00	-0.01	0.01
95% CI (lower to upper)	(-0.004 to 0.013)		(0.001 to 0.008)							

In anterior cingulate gyrus, among patient group, the mean FA was decreased ipsilaterally compared to their contralateral side significantly. However, the mean of side-to-side difference of FA of cases did not differ significantly from controls side to side difference of FA. Although the ipsilateral and contralateral FA of cases was decreased compared to those of controls, they did not show statistically significant difference.

Figure 20: comparison of anterior cingulate gyrus FA between patients and controls

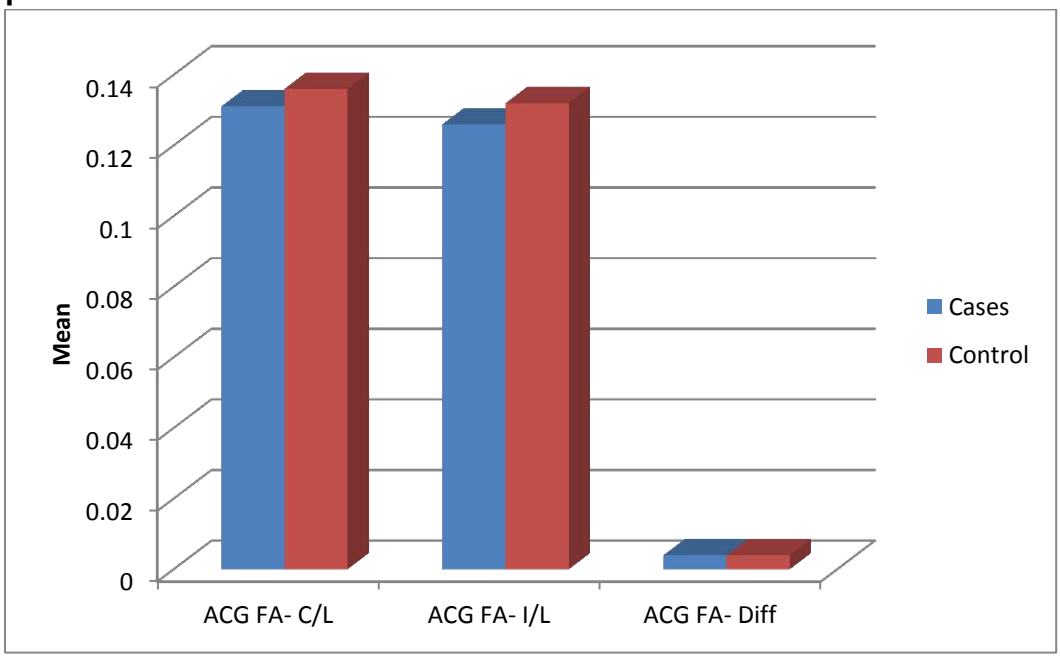


Table 14: comparison of anterior cingulate gyrus ADC between patients and controls

Site	Cases		Control		t	p-value	Difference		95% CI of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
ACG ADC- I/L	1.038	0.138	1.018	0.075	0.473	0.640	0.02	0.04	-0.07	0.10
ACGADC-C/L	0.981	0.083	0.973	0.061	0.312	0.758	0.01	0.03	-0.05	0.06
ACG ADC- Diff	0.056	0.100	0.045	0.024	0.412	0.684	0.01	0.03	-0.04	0.07
95% CI (lower to upper)	(0.003 to 0.109)		(0.031 to 0.059)							

In anterior cingulate gyrus, among patient group, the mean ADC was higher significantly on ipsilateral side compared to their contralateral side. However, the mean of side-to-side difference of ADC of cases did not differ significantly from controls side to side difference of ADC. Although the ipsilateral and contralateral ADC of cases was increased compared to those of controls, they did not show statistically significant difference.

Figure 21: comparison of anterior cingulate gyrus ADC between patients and controls

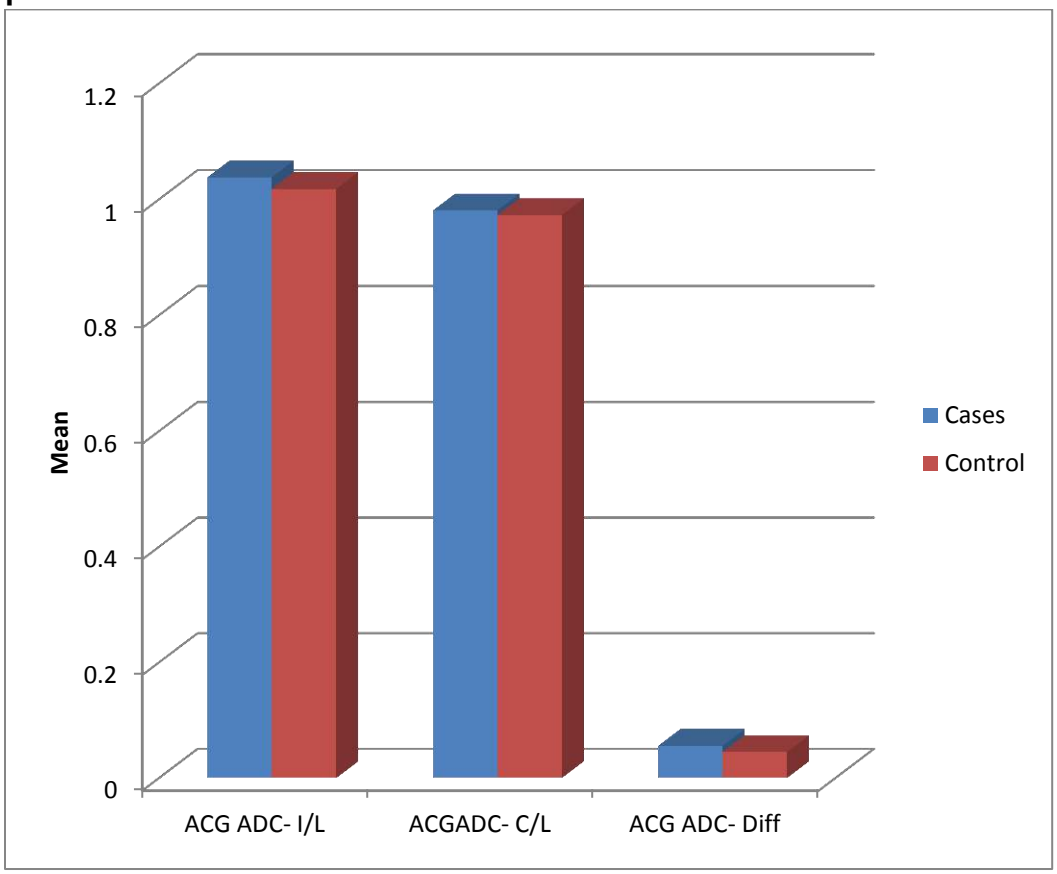


Table 15: comparison of posterior cingulate gyrus FA between patients and controls

Site	Cases		Control		t	p-value	Difference		95% CI of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
PCG FA- C/L	0.156	0.020	0.157	0.017	-0.221	0.827	0.00	0.01	-0.02	0.01
PCG FA- I/L	0.142	0.018	0.152	0.015	-1.652	0.110	-0.01	0.01	-0.02	0.00
PCG FA- Diff	0.014	0.013	0.005	0.005	2.424	**0.022**	0.01	0.00	0.00	0.02
95% CI (lower to upper)	(0.007 to 0.020)		(0.002 to 0.008)							

In posterior cingulate gyrus, among patient group, the ipsilateral mean FA was decreased compared to their contralateral side significantly. Also, the mean of side-to-side difference of FA of cases was higher than the side-to-side difference of FA of controls and showed statistically significant difference. Although the ipsilateral and contralateral FA of cases was decreased compared to those of controls, they did not show statistical significance.

Figure 22: comparison of posterior cingulate gyrus FA between patients and controls

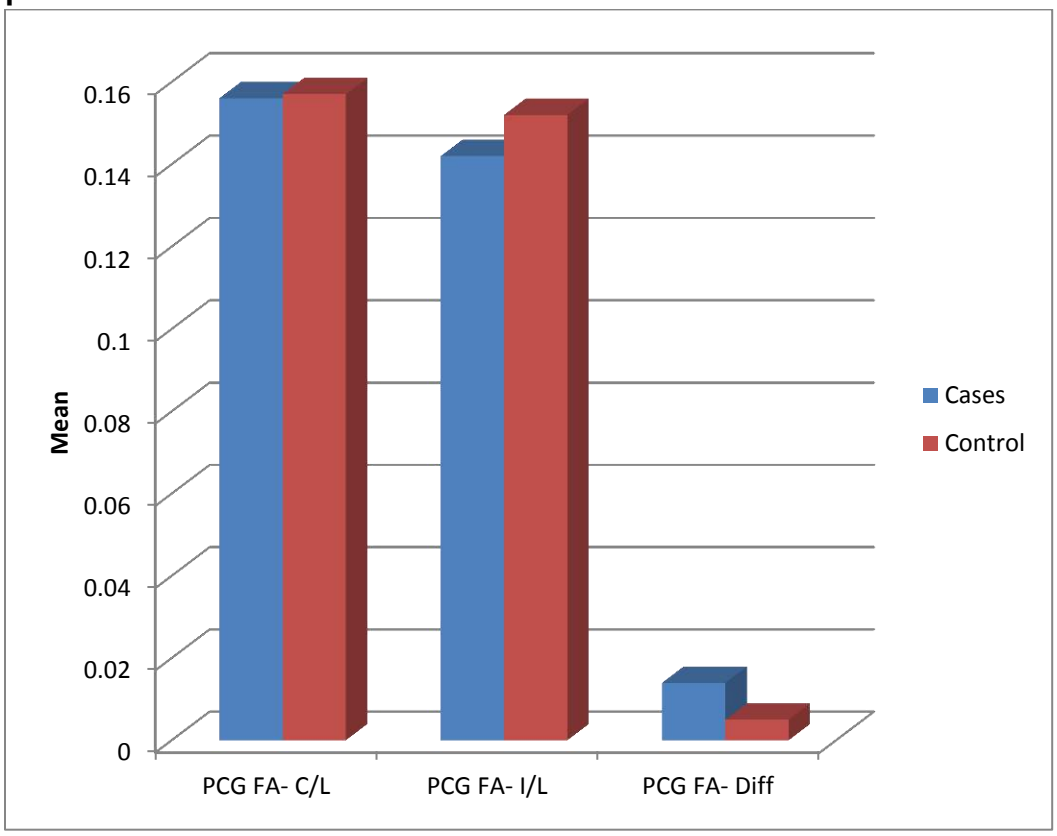


Table 16: comparison of posterior cingulate gyrus ADC between patients and controls

Site	Cases		Control		t	p-value	Difference		95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
PCG ADC- I/L	1.041	0.223	1.012	0.076	0.454	0.653	0.03	0.06	-0.10	0.16
PCG ADC- C/L	0.973	0.213	0.990	0.074	-0.282	0.780	-0.02	0.06	-0.14	0.11
PCG ADC- Diff	0.068	0.048	0.022	0.019	3.332	**0.002**	0.05	0.01	0.02	0.07
95% CI (lower to upper)	(0.042 to 0.093)		(0.011 to 0.033)							

In posterior cingulate gyrus, among patient group, the ipsilateral mean ADC was increased compared to their contralateral side significantly. Also, the mean of side-to-side difference of ADC of cases was higher than the side-to-side difference of ADC of controls and showed statistically significant difference. Although the ipsilateral ADC of cases was increased compared to controls, it did not show statistical significance. Whereas the contralateral mean ADC of cases wass less than the controls mean ADC but did not show statistical significance.

Figure 23: comparison of posterior cingulate gyrus ADC between patients and controls

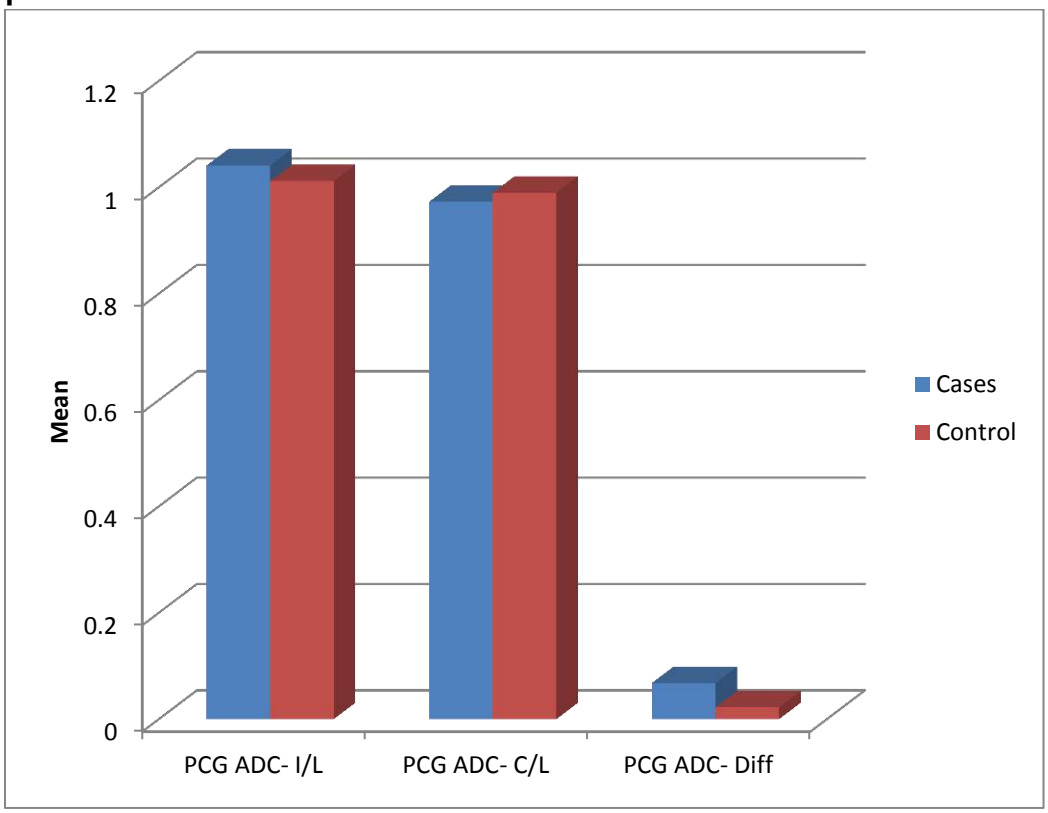


Table 17: comparison of optic radiation FA between patients and controls

Site	Cases		Control		t	p-value	Difference		95% CI of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
Optic Radiation FA-C/L	0.389	0.031	0.404	0.038	-1.174	0.250	-0.01	0.01	-0.04	0.01
Optic Radiation FA-I/L	0.369	0.037	0.375	0.035	-0.425	0.674	-0.01	0.01	-0.03	0.02
Optic Radiation FA-Diff	0.019	0.025	0.029	0.024	-1.024	0.315	-0.01	0.01	-0.03	0.01
95% CI (lower to upper)	(0.006 to 0.033)		(0.015 to 0.042)							

In the optic radiation, among patient group, the mean FA was decreased ipsilaterally compared to their contralateral side significantly. But the mean of side-to-side difference of FA of cases did not differ significantly from side-to-side difference of FA of controls. Although both ipsilateral and contralateral FA of cases was decreased compared to those of controls, the difference was not statistically significant.

Figure 24: comparison of optic radiation FA between patients and controls

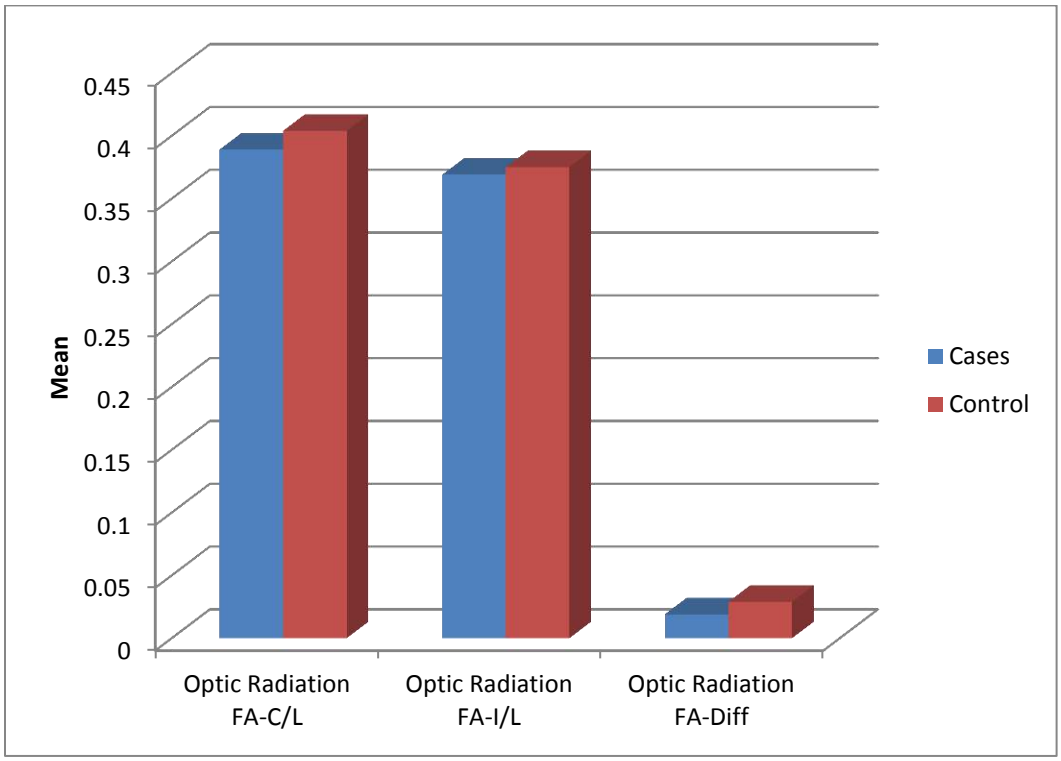


Table 18: comparison of optic radiation ADC between patients and controls

Site	Cases		Control		t	p-value	Difference		95% CI of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
Optic Radiation ADC- I/L	0.951	0.095	0.946	0.104	0.152	0.880	0.01	0.04	-0.07	0.08
Optic Radiation ADC-C/L	0.899	0.072	0.901	0.068	-0.080	0.937	0.00	0.03	-0.05	0.05
Optic Radiation ADC-Diff	0.052	0.063	0.044	0.061	0.334	0.741	0.01	0.02	-0.04	0.05
95% CI (lower to upper)	(0.018 to 0.086)		(0.009 to 0.079)							

In the optic radiation, among patient group, the mean ADC was increased ipsilaterally compared to their contralateral side significantly. However, the mean of side-to-side difference of ADC of cases did not differ significantly from side-to-side difference of ADC of controls. The mean ADC of ipsilateral side of cases was increased compared to controls but did not show statistical significance. Whereas the mean of contralateral ADC of cases is less compared to controls but did not differ significantly.

Figure 25: comparison of optic radiation ADC between patients and controls

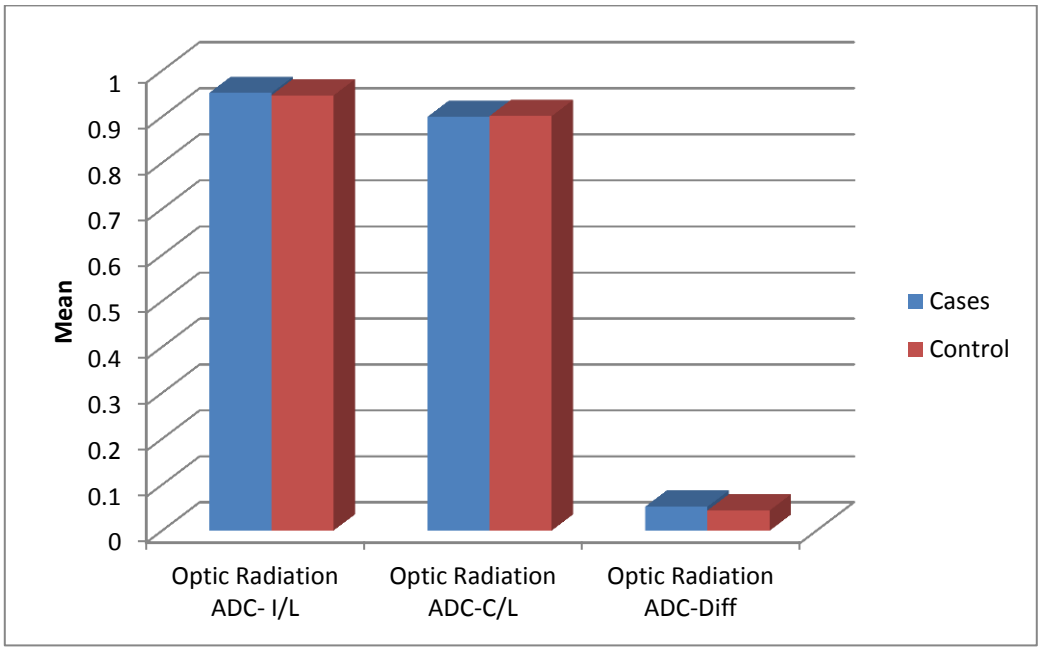


Table 19: comparison of fornix FA between patients and controls

Site	Cases		Control		T	p-value	Difference		95% CI of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
Fornix FA- C/L	0.216	0.038	0.220	0.031	-0.343	0.734	0.00	0.01	-0.03	0.02
Fornix FA- I/L	0.193	0.038	0.208	0.031	-1.152	0.259	-0.01	0.01	-0.04	0.01
Fornix FA- Diff	0.023	0.015	0.012	0.007	2.329	**0.027**	0.01	0.00	0.00	0.02
95% CI (lower to upper)	(0.014 to 0.031)		(0.008 to 0.016)							

In fornix, among patients mean FA is significantly decreased ipsilaterally when compared to their contralateral FA. When compared to controls, the mean of side-to-side difference of FA values of cases is significantly higher with ipsilateral being less than contralateral side. The mean FA of both ipsilateral and contralateral sides of cases was decreased compared to controls but did not show statistical significance.

Figure 26: comparison of fornix FA between patients and controls

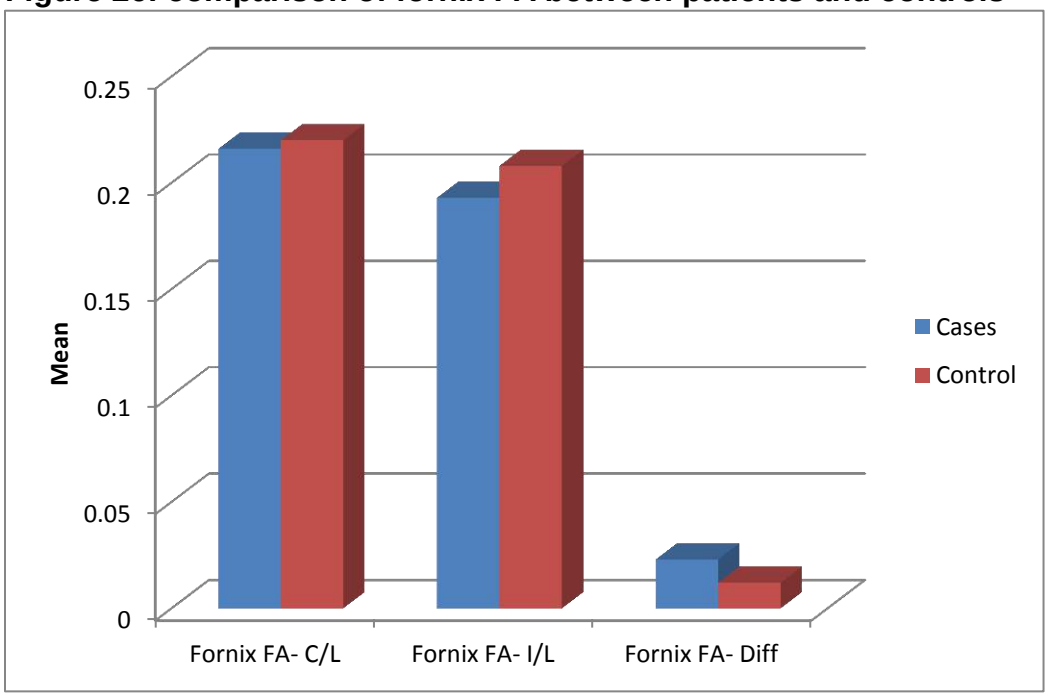


Table 20: comparison of fornix ADC between patients and controls

Site	Cases		Control		t	p-value	Difference		95% CI of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
Fornix ADC-I/L	1.857	0.450	1.537	0.371	2.105	**0.044**	0.32	0.15	0.01	0.63
Fornix ADC-C/L	1.732	0.426	1.452	0.333	1.982	0.057	0.28	0.14	-0.01	0.57
Fornix ADC-Diff	0.125	0.144	0.085	0.084	0.909	0.371	0.04	0.04	-0.05	0.13
95% CI (lower to upper)	(0.048 to 0.202)		(0.036 to 0.134)							

In fornix, among patient group, the mean ADC of ipsilateral side was increased compared to contralateral side significantly. The mean of side-to-side difference of ADC of cases although higher than side-to-side difference of ADC of controls, did not reach statistical significance. The ipsilateral ADC of cases was increased compared to controls with statistical significance. Whereas on the contralateral side of patients the mean ADC was increased compared to controls, and showed trend towards significance. significance.

Figure 27: comparison of fornix ADC between patients and controls

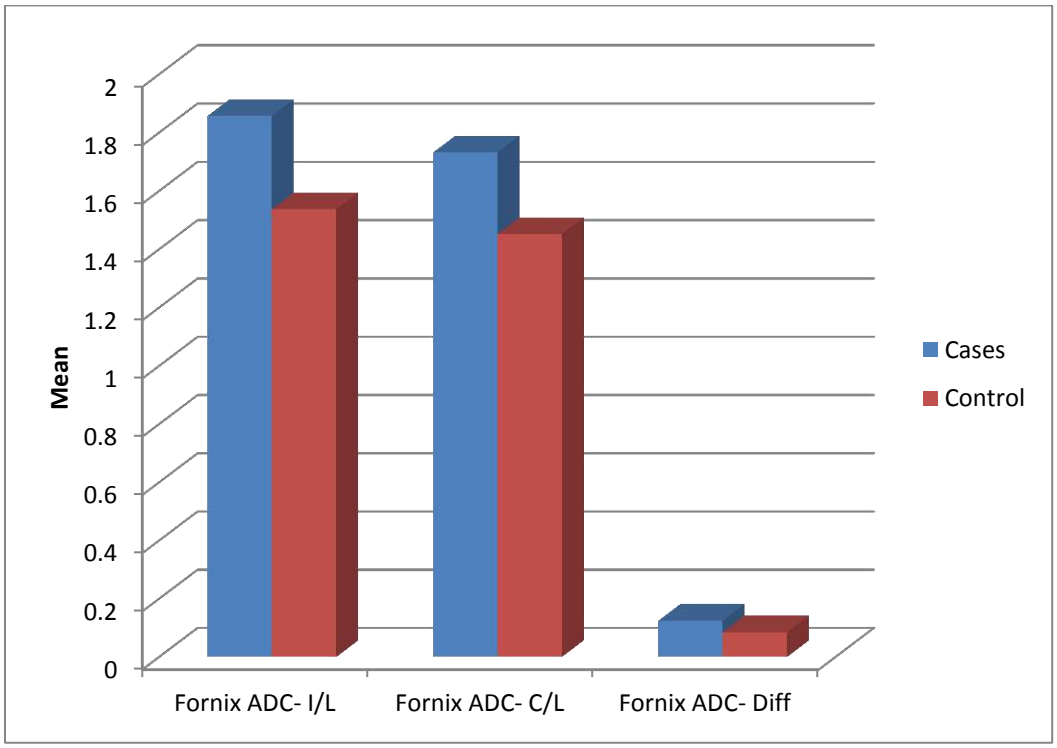


Table 21: comparison of uncinate fasciculus FA between patients and controls

Site	Cases		Control		t	p-value	Difference		95% CI of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
UF FA-C/L	0.216	0.029	0.227	0.020	-1.185	0.246	-0.01	0.01	-0.03	0.01
UF FA-I/L	0.195	0.022	0.216	0.019	-2.838	**0.008**	-0.02	0.01	-0.04	0.01
UF FA-Diff	0.021	0.018	0.011	0.007	2.060	**0.049**	0.01	0.01	0.00	0.02
95%CI (lower to upper)	(0.012 to 0.031)		(0.006 to0.015)							

In uncinate fasciculus, among patient group, mean FA of ipsilateral side was significantly less than contralateral side. Also, the mean of side-to-side difference of FA values was significantly higher in cases compared to side-to-side difference of FA in controls. The ipsilateral mean FA of UF in cases was significantly reduced compared to controls. But the contralateral mean FA of patients did not differ significantly from controls although mean values is reduced. These indicate decreased FA of uncinate fasciculus bilaterally in patients with statistical significance on ipsilateral side.

Figure 28: comparison of uncinate fasciculus FA between patients and controls

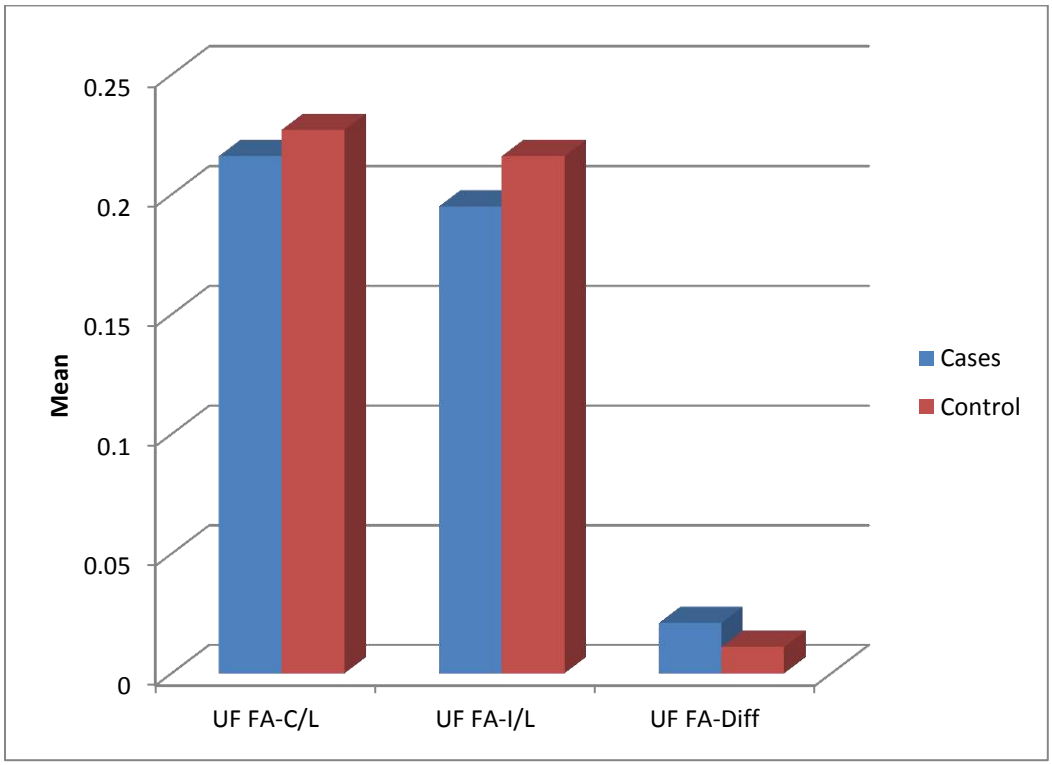


Table 22: comparison of uncinate fasciculus ADC between patients and controls

Site	Cases		Control		t	p-value	Difference		95% CI of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
UF ADC-I/L	1.104	0.096	1.041	0.088	1.844	0.076	0.06	0.03	-0.01	0.13
UF ADC- C/L	1.031	0.071	1.023	0.095	0.277	0.784	0.01	0.03	-0.05	0.07
UF ADC-Diff	0.073	0.052	0.019	0.025	3.556	**0.001**	0.05	0.02	0.02	0.09
95% CI (lower to upper)	(0.045 to 0.100)		(0.004 to 0.033)							

In uncinate fasciculus, among patient group, the mean ADC of ipsilateral side was increased compared to contralateral side significantly. Also, the mean of side-to-side difference of ADC of cases was higher than side-to-side difference of ADC of controls, with statistical significance. The ipsilateral ADC of cases was increased compared to controls with a trend towards statistical significance (p=0.07). Whereas on the contralateral side of patients the mean ADC is increased compared to controls but did not show statistical significance.

Figure 29: comparison of uncinate fasciculus ADC between patients and controls

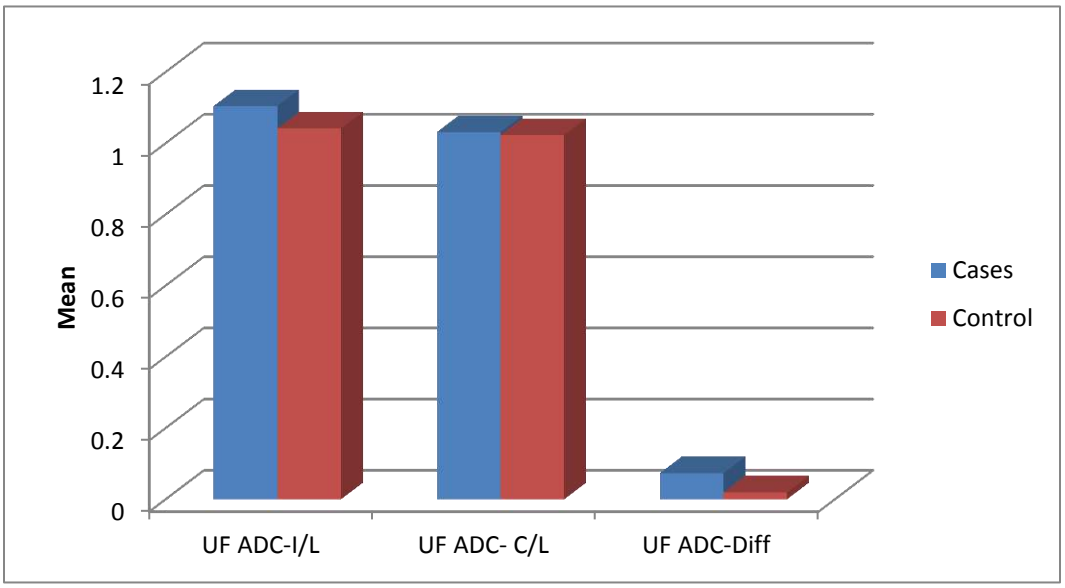


Table 23: comparison of arcuate fasciculus FA between patients and controls

Site	Cases		Control		t	p-value	Difference		95% CI of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
Arcuate fasciculus FA-C/L	0.229	0.027	0.241	0.034	-1.084	0.288	-0.01	0.01	-0.04	0.01
Arcuate fasciculus FA-I/L	0.189	0.017	0.226	0.038	-3.547	**0.001**	-0.04	0.01	-0.06	-0.02
Arcuate fasciculus FA-Diff	0.040	0.020	0.015	0.011	4.160	**0.000**	0.03	0.01	0.01	0.04
95% CI (lower to upper)	(0.029 to 0.051)		(0.009 to 0.021)							

In arcuate fasciculus, among patient group, mean FA of ipsilateral side was significantly less than contralateral side. Also, the mean of side-to-side difference of FA values was significantly higher in cases compared to side-to-side difference of FA in controls. The ipsilateral mean FA of arcuate fasciculus in cases was significantly reduced compared to controls. But the contralateral mean FA of patients did not differ significantly from controls although mean value is reduced. These indicate decreased FA of arcuate fasciculus bilaterally in patients with statistical significance on ipsilateral side.

Figure 30: comparison of arcuate fasciculus FA between patients and controls

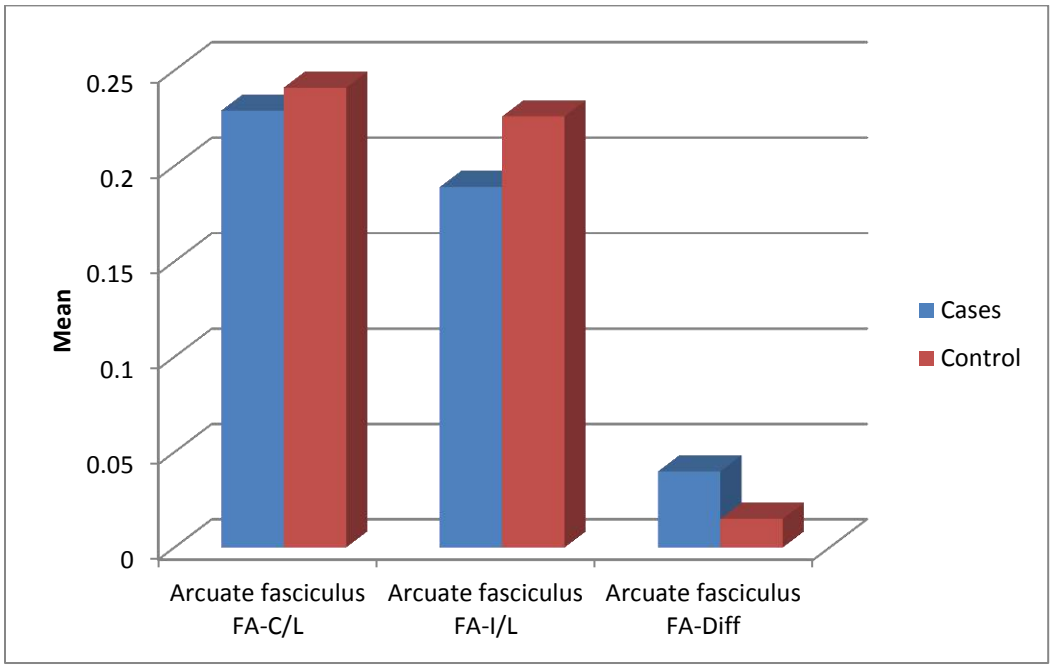


Table 24: comparison of arcuate fasciculus ADC between patients and controls

Site	Cases		Control		t	p-value	Difference		95% CI of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
Arcuate fasciculus ADC I/L	0.963	0.046	0.926	0.062	1.902	0.068	0.04	0.02	-0.00	0.09
Arcuate fasciculus ADC C/L	0.919	0.054	0.916	0.062	0.143	0.887	0.00	0.02	-0.04	0.05
Arcuate fasciculus ADC-Diff	0.044	0.061	0.010	0.007	2.093	**0.046**	0.03	0.02	0.00	0.07
95 % CI (lower to upper)	(0.012 to 0.077)		(0.006 to 0.014)							

In arcuate fasciculus, among patient group, the mean ADC of ipsilateral side was increased compared to contralateral side significantly. Also, the mean of side-to-side difference of ADC of cases was higher than side-to-side difference of ADC of controls, with statistical significance. The ipsilateral ADC of cases is increased compared to controls with a trend towards statistical significance (p=0.06). Whereas on the contralateral side of patients the mean ADC is increased compared to controls but did not show statistical significance.

Figure 31: comparison of arcuate fasciculus ADC between patients and controls

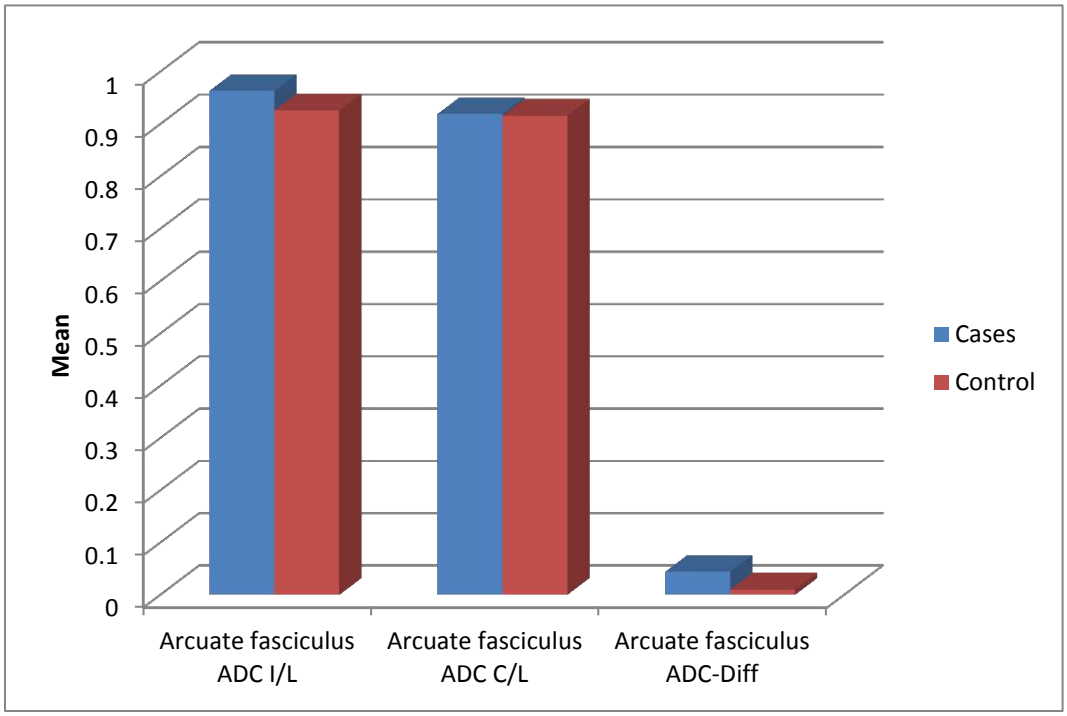


Table 25: comparison of superior longitudinal fasciculus FA between patients and controls

Site	Cases		Control		t	p-value	Difference		95% CI of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
SLF FA- C/L	0.227	0.036	0.229	0.032	-0.135	0.894	0.00	0.01	-0.03	0.02
SLF FA- I/L	0.206	0.032	0.214	0.022	-0.719	0.478	-0.01	0.01	-0.03	0.01
SLF FA- Diff	0.021	0.017	0.015	0.017	0.896	0.378	0.01	0.01	-0.01	0.02
95% CI (lower to upper)	(0.012 to 0.030)		(0.005 to 0.025)							

In superior longitudinal fasciculus, among patient group, the mean FA was decreased ipsilaterally compared to their contralateral side significantly. Although the mean of side-to-side difference of FA of cases was higher than side-to-side difference of FA of controls, it did not reach statistical significance. Although both ipsilateral and contralateral FA of cases was decreased compared to those of controls, the difference was not statistically significant.

Figure 32: comparison of superior longitudinal fasciculus FA between patients and controls

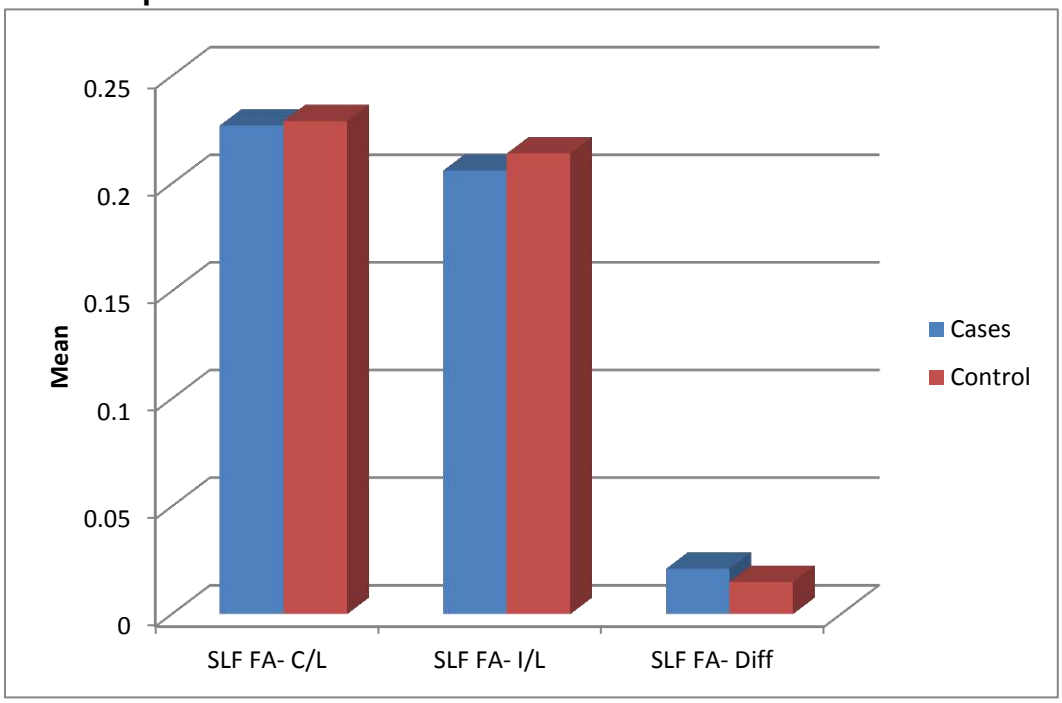


Table 26: comparison of superior longitudinal fasciculus ADC between patients and controls

Site	Cases		Control		t	p-value	Difference		95% CI of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
SLF ADC- I/L	1.009	0.079	1.003	0.093	0.188	0.852	0.01	0.03	-0.06	0.07
SLF ADC- C/L	0.959	0.065	0.956	0.076	0.142	0.888	0.00	0.03	-0.05	0.06
SLF ADC- Diff	0.049	0.063	0.047	0.029	0.123	0.903	0.00	0.02	-0.04	0.04
95% CI (lower to upper)	(0.016 to 0.083)		(0.031 to 0.064)							

In superior longitudinal fasciculus, among patient group, the mean ADC was increased ipsilaterally compared to their contralateral side significantly. Although the mean of side-to-side difference of ADC of cases was higher than side-to-side difference of FA of controls, it did not reach statistical significance. Also, both ipsilateral and contralateral ADC of cases is increased compared to those of controls, but the not statistically significant.

Figure 33: comparison of superior longitudinal fasciculus ADC between patients and controls

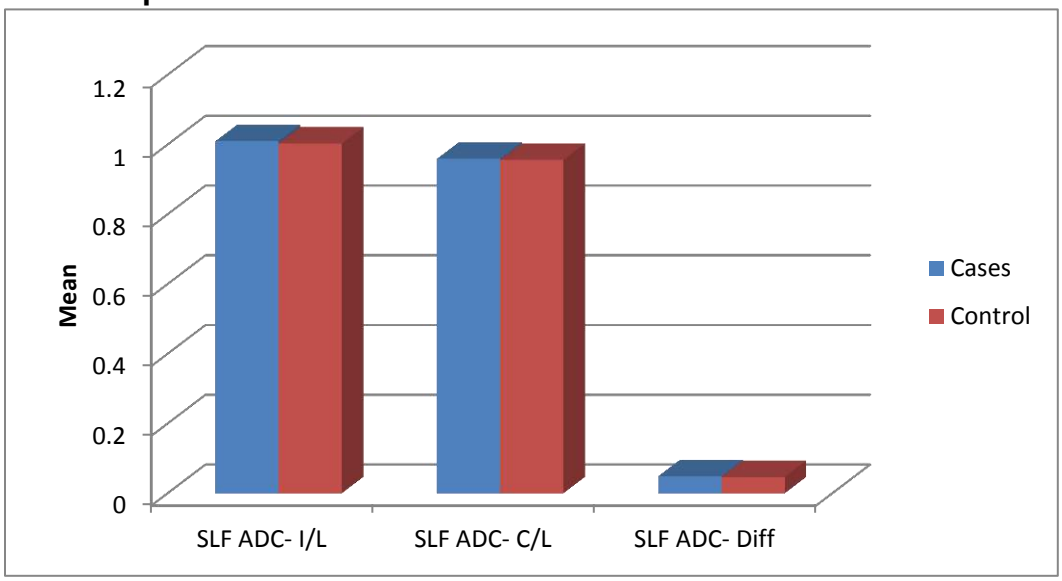


Table 27: comparison of inferior longitudinal fasciculus FA between patients and controls

Site	Cases		Control		t	p-value	Difference		95% CI of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
ILF FA-C/L	0.293	0.029	0.294	0.046	-0.083	0.934	-0.00	0.01	-0.03	0.03
ILF FA- I/L	0.236	0.031	0.265	0.037	-2.327	**0.027**	-0.03	0.01	-0.05	-0.00
ILF FA- Diff	0.057	0.020	0.029	0.017	4.064	**0.000**	0.03	0.01	0.01	0.04
95% CI (lower to upper)	(0.046 to 0.067)		(0.020 to 0.039)							

In inferior longitudinal fasciculus, among patient group, mean FA of ipsilateral side was significantly less than contralateral side. Also, the mean of side-to-side difference of FA values of cases was significantly higher than side-to-side difference of FA in controls. The ipsilateral mean FA of ILF in cases was significantly reduced compared to controls. But the contralateral mean FA of patients did not differ significantly from controls although mean value is reduced. These indicate decreased FA of ILF bilaterally in patients with ipsilateral FA decrease being statistically significant.

Figure 34: comparison of inferior longitudinal fasciculus FA between patients and controls

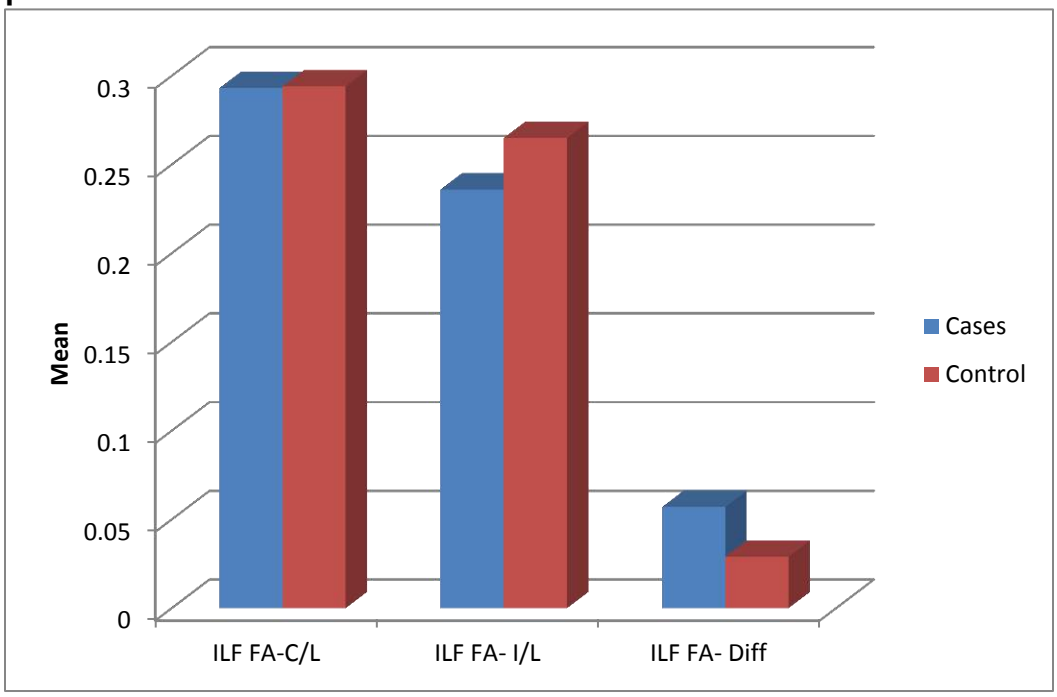


Table 28: comparison of inferior longitudinal fasciculus ADC between patients and controls

Site	Cases		Control		t	p-value	Difference		95% CI of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
ILF ADC- I/L	0.917	0.042	0.886	0.042	2.000	0.055	0.03	0.02	-0.00	0.06
ILF ADC- C/L	0.862	0.040	0.869	0.033	-0.550	0.587	-0.01	0.01	-0.04	0.02
ILF ADC- Diff	0.055	0.022	0.017	0.014	5.620	**0.000**	0.04	0.01	0.02	0.05
95% CI (lower to upper)	(0.043 to 0.067)		(0.009 to 0.025)							

In inferior longitudinal fasciculus, among patient group, the mean ADC of ipsilateral side was increased compared to contralateral side significantly. Also, the mean of side-to-side difference of ADC of cases was higher than side-to-side difference of ADC of controls, with statistical significance. The ipsilateral ADC of cases was increased compared to controls with a trend towards statistical significance(p=0.05). Whereas on the contralateral side of patients the mean ADC was less compared to controls but did not show statistical significance.

Figure 35: comparison of inferior longitudinal fasciculus ADC between patients and controls

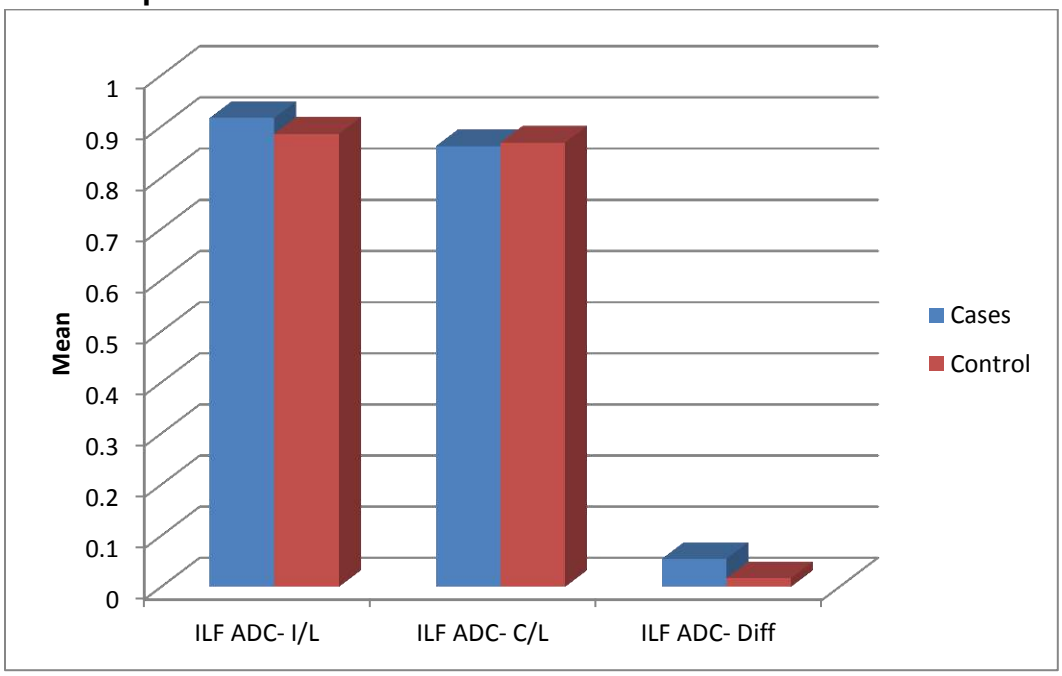


Table 29: comparison of inferior fronto-occipital fasciculus FA between patients and controls

Site	Cases		Control		t	p-value	Difference		95% CI of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
IFO FA- C/L	0.270	0.015	0.283	0.024	-1.766	0.088	-0.01	0.01	-0.03	0.00
IFO FA- I/L	0.256	0.022	0.265	0.018	-1.179	0.249	-0.01	0.01	-0.02	0.01
IFO FA- Diff	0.014	0.017	0.018	0.012	-0.754	0.457	0.00	0.01	-0.02	0.01
95% CI (lower to upper)	(0.005 to 0.023)		(0.011 to 0.025)							

In the inferior fronto-occipital fasciculus, among patient group, the mean FA was decreased ipsilaterally compared to their contralateral side significantly. However, the mean of side-to-side difference of FA of cases was less compared to side-to-side difference of FA of controls and did not show any statistical significance. Although both ipsilateral and contralateral FA of cases is decreased compared to those of controls, the difference was not statistically significant.

Figure 36: comparison of inferior fronto-occipital fasciculus FA between patients and controls

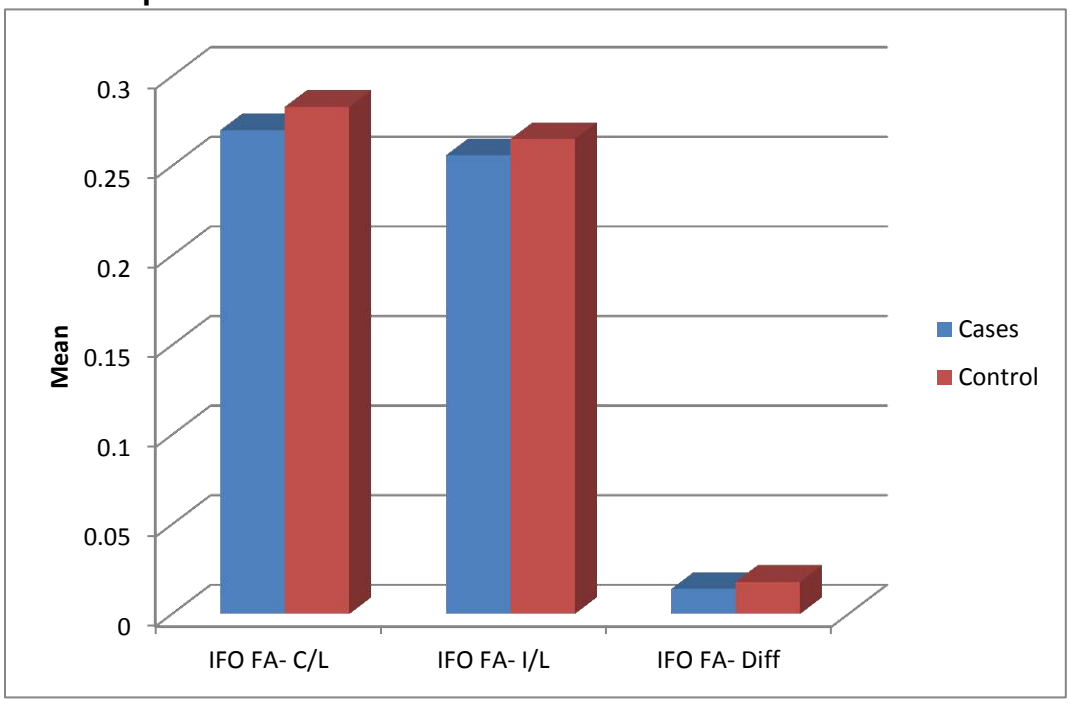


Table 30: comparison of inferior fronto-occipital fasciculus ADC between patients and controls

Site	Cases		Control		t	p-value	Difference		95% CI of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
IFO ADC- I/L	0.988	0.095	0.993	0.077	-0.168	0.868	-0.01	0.03	-0.07	0.06
IFO ADC- C/L	0.981	0.086	0.970	0.078	0.372	0.713	0.01	0.03	-0.05	0.07
IFO ADC- Diff	0.006	0.062	0.023	0.018	-0.964	0.343	-0.02	0.02	-0.05	0.02
95% CI (lower to upper)	(-0.027 to 0.039)		(0.013 to 0.033)							

In the inferior fronto-occipital fasciculus, among patient group, the mean ADC was increased ipsilaterally compared to their contralateral side but not significantly. Also the mean of side-to-side difference of ADC of cases was less compared to side-to-side difference of ADC of controls but did not show any statistical significance. The mean ADC of ipsilateral side of patients was less than controls mean ADC but not statistically significant. Whereas on the contralateral side ADC of cases was increased compared to those of controls, but is not statistically significant.

Figure 37: comparison of inferior fronto-occipital fasciculus ADC between patients and controls

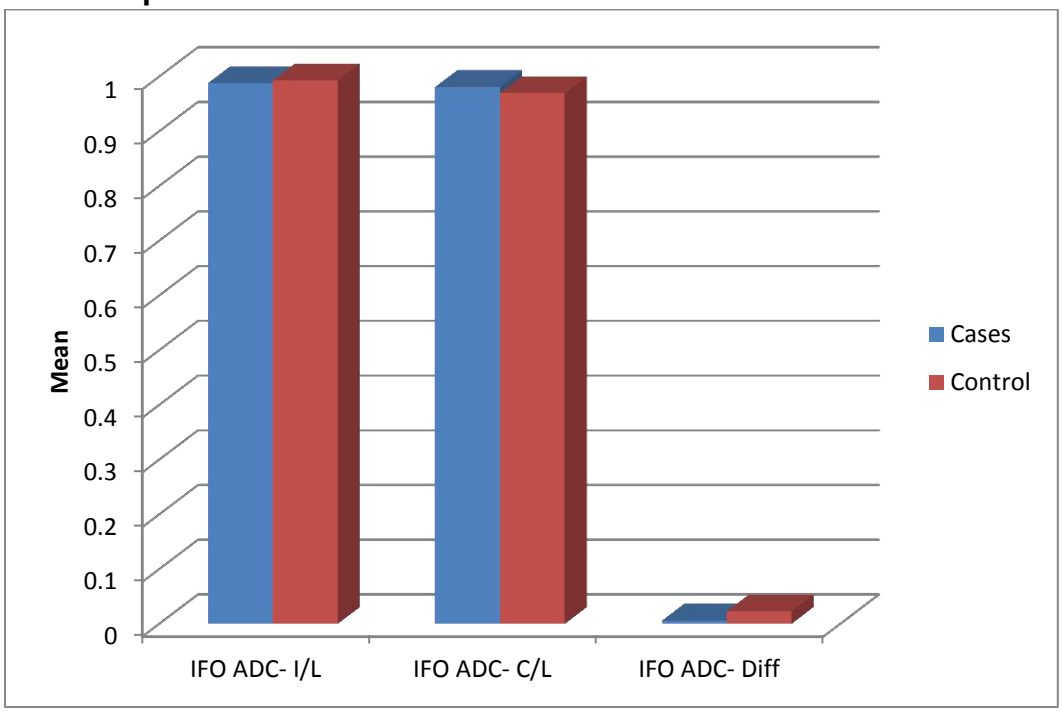


Table 31: Comparison of ipsilateral versus contralateral FA of different region of interest in patients:

FA - Site	C/L		I/L		t	p-value	Difference		95% CI of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
Hippocampus	0.175	0.017	0.158	0.015	9.277	0.000*	0.02	0.01	0.01	0.02
PHG	0.166	0.018	0.151	0.017	8.930	0.000*	0.01	0.01	0.01	0.02
Caudate	0.159	0.023	0.156	0.020	1.159	0.256	0.00	0.01	0.00	0.01
Thalamus	0.292	0.019	0.279	0.023	6.747	0.000*	0.01	0.01	0.01	0.02
External capsule	0.299	0.036	0.262	0.027	5.511	0.000*	0.04	0.03	0.02	0.05
ACG	0.133	0.012	0.129	0.014	1.898	0.068	0.00	0.01	0.00	0.01
PCG	0.156	0.018	0.147	0.017	4.966	0.000*	0.01	0.01	0.01	0.01
Optic Radiation	0.396	0.035	0.372	0.036	5.277	0.000*	0.02	0.02	0.01	0.03
Fornix	0.218	0.034	0.200	0.035	7.416	0.000*	0.02	0.01	0.01	0.02
Uncinate Fasciculus	0.216	0.029	0.195	0.022	4.764	0.000*	0.02	0.02	0.01	0.03
Arcuate fasciculus	0.229	0.027	0.189	0.017	8.000	0.000*	0.04	0.02	0.03	0.05
SLF	0.228	0.034	0.210	0.028	5.765	0.000*	0.02	0.02	0.01	0.02
ILF	0.293	0.029	0.236	0.031	11.429	0.000*	0.06	0.02	0.05	0.07
IFO	0.271	0.015	0.256	0.021	3.505	0.003*	0.01	0.02	0.01	0.02

In comparison of ipsilateral versus contralateral FA values among patients, ipsilateral FA was significantly reduced compared to contralateral side in Hippocampus, ParaHippocampus, Thalamus, Posterior Cingulate, Optic radiation, Fornix, Uncinate fasciculus, Superior & Inferior Longitudinal fasciculus, Inferior FrontoOccipital fasciculus. However, there was no statistically significant difference between two sides in caudate and anteriror cingulate gyrus

Figure 38: Comparison of ipsilateral versus contralateral FA of different region of interest in patients

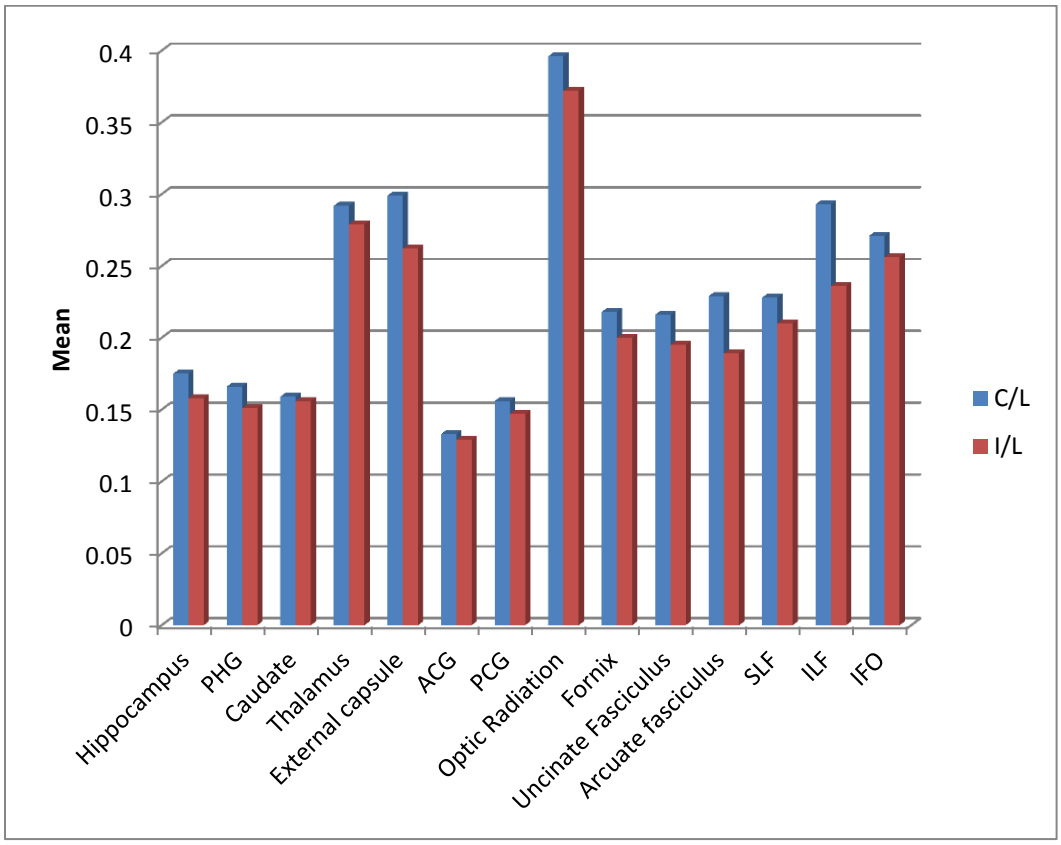
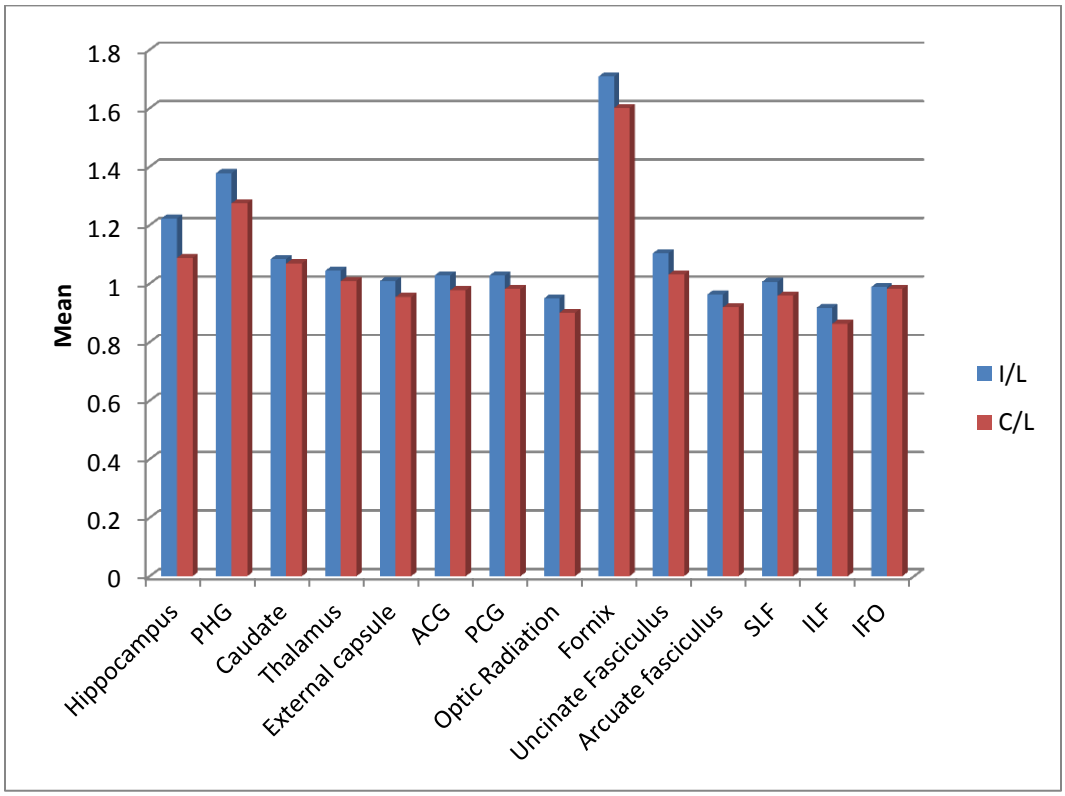


Table 32: Comparison of ipsilateral versus contralateral ADC of different region of interest in patients :

ADC - Site	I/L		C/L		t	p-value	Difference		95% CI of the Difference	
	Mean	SD	Mean	SD			Mean	SD	Lower	Upper
Hippocampus	1.223	0.150	1.088	0.102	5.204	0.000*	0.13	0.11	0.08	0.19
PHG	1.378	0.136	1.275	0.150	6.973	0.000*	0.10	0.08	0.07	0.13
Caudate	1.084	0.302	1.069	0.287	0.885	0.389	0.01	0.07	-0.02	0.05
Thalamus	1.044	0.112	1.009	0.107	5.263	0.000*	0.03	0.04	0.02	0.05
External capsule	1.009	0.090	0.954	0.078	5.563	0.000*	0.06	0.04	0.03	0.08
ACG	1.028	0.112	0.977	0.072	3.798	0.001*	0.05	0.07	0.02	0.08
PCG	1.027	0.169	0.981	0.161	5.876	0.000*	0.05	0.04	0.03	0.06
Optic Radiation	0.949	0.098	0.900	0.069	4.330	0.000*	0.05	0.06	0.03	0.07
Fornix	1.708	0.439	1.601	0.405	4.856	0.000*	0.11	0.12	0.06	0.15
Uncinate Fasciculus	1.104	0.096	1.031	0.071	5.623	0.000*	0.07	0.05	0.05	0.10
Arcuate fasciculus	0.963	0.046	0.919	0.054	2.910	0.011	0.04	0.06	0.01	0.08
SLF	1.006	0.084	0.958	0.069	5.411	0.000*	0.05	0.05	0.03	0.07
ILF	0.917	0.042	0.862	0.040	10.184	0.000*	0.06	0.02	0.04	0.07
IFO	0.988	0.095	0.981	0.086	0.402	0.693	0.01	0.06	-0.03	0.04

In comparison of ipsilateral versus contralateral ADC values among patients, ipsilateral ADC was significantly increased compared to contralateral side in Hippocampus, ParaHippocampus, Thalamus, External capsule, Anterior & Posterior Cingulate gyrus, Optic radiation, Fornix, Uncinate fasciculus, Superior & Inferior Longitudinal Fasciculus. However, there was no statistically significant difference between two sides in caudate, arcuate fasciculus and inferior fronto-occipital fasciculus.

Figure 39: Comparison of ipsilateral versus contralateral ADC of different region of interest in patients:



DISCUSSION

Epilepsy is the tendency to have unprovoked seizures. About 1% of people worldwide are suffering from epilepsy.

According to the International League Against Epilepsy (ILAE) official report in 2014, epilepsy should be considered in any of the following conditions: two or more seizures occurring >24 hours apart, one unprovoked seizure and a probability of recurrent seizure risk over 60%, and diagnosis of an epilepsy syndrome[2]. If there is any epileptiform discharge on electroencephalography, or a potential epileptogenic structure on brain imaging, the probability of recurrent epileptic seizure exceeds 60%[3].

The term Temporal lobe epilepsy (TLE) was included in the classification of the ILAE in 1989 under the group of “localization-related symptomatic epilepsies characterized by seizures with specific modes of precipitation”[4].

Temporal lobe epilepsy is the most common form of focal epilepsy. Major focus of seizure activity in TLE is hippocampus and microstructural alterations take place even before they can be seen in conventional imaging[48].

In ictal phase of seizures, oxygen consumption of seizure focus increases, which is more than the increased blood flow. The resulting relative ischemia and cytotoxic edema result in decreased ADC. With progression of time, epilepsy eventually results in neuroglia, increased extracellular space and increased interictal ADC[61]. White matter tracts through which the epileptiform discharges travel will have decreased anisotropic diffusion, resulting in reduced fractional anisotropy (FA)[61].
Diffusion tensor imaging is sensitive to identify these abnormalities with its arsenal of indices.

In our study we have used the FA and ADC or MD values of the hippocampi and various other temporal and extratemporal grey and white matter tracts to study the hippocampal and extra hippocampal alterations in temporal lobe epilepsy patients.

The cases group consisted 16 patients with mean age of 29 years(±9years) among whom 10 were males (63%) and 6 were females (37%), all the patients were diagnosed as unilateral mesial temporal lobe epilepsy based on EEG localised to the ipsilateral temporal lobe and MRI epilepsy protocol showing hippocampal sclerosis (except 2 cases who had normal MRI).

The disease duration varied from 4 years to 40 years with mean duration of 16years (±9years).

The controls group consisted of 14 subjects with mean age of 33years(±9years), among whom 7 were males (50%) and 7 were females (50%), with none having history of any seizure or focal neurological deficit with conventional MRI scan showing normal study.

Temporal & limbic lobe mean diffusivity and fractional anisotropy:

In our study, patients **hippocampus** FA and MD side-to-side difference was significantly higher compared to controls and ipsilateral FA decrease and MD increase were significant compare to contralateral side among patient group. These are in line with a study done by T.M. Salmenpera et al with 13 controls and 7 unilateral TLE patients (6 with hippocampal sclerosis, 1 with normal MRI), were compared. They found that MD asymmetry indexes were significantly different between the patient and control groups and concluded that hippocampal MD changes are more sensitive than FA changes in detecting the epileptogenic side[62].

Asmaa M. Ebraheim et al[50] in their study found that FA differences between both hippocampi in patients group were significantly increased compared to controls and concluded that hippocampal abnormalities even in patients with normal MRI can be used to lateralise seizure and improve diagnostic accuracy before epilepsy surgery.

In our study compared to controls, ipsilateral MD of patients was significantly higher, whereas ipsilateral FA showed only a trend towards significance. The results of our ipsilateral hippocampus is in line with the results of Assaf et al[48] in 2003 who also found increased mean diffusitivity of ipsilateral hippocampus with ipsilateral FA being decreased, but the difference didnot attain statistical significance (*P* =.08). Some ROI-based studies of the hippocampus found MD to be more sensitive than FA for lateralizing mTLE (Assaf et al[48]., 2003; Salmenpera et al[62]., 2006) which is similar to our study result. This can be suggesting that expansion of the extracellular space may be occurring which causes altered MD, while tissue organization is still relatively preserved reflected by FA.

In our study, patients **parahippocampal gyrus (PHG)** FA and MD side-to-side difference was significantly higher than controls and ipsilateral values altered significantly in comparison to patient contralateral side and control mean values which signifies involvement of PHG on side of epileptogenic focus. These are in line with results of study by Ahmadi et al[10].and Thivard et al[63]. where ipsilateral PHG showed altered DTI metrics in comparison to controls but contralateral FA did not show significant alterations than controls.

The **Fornix** in our patient group revealed significant side-to-side difference of FA in comparison to controls. When compared to controls the bilateral fornix showed altered MD with ipsilateral being significant, and contralateral showing trend towards significance. But mean of side-to-side difference of ADC did not alter significantly between two groups. The FA and MD values are significantly altered in ipsilateral fornix compared to contralateral side among our patient group. These indicate that fornix is mainly involved ipsilaterally in our TLE patient group. Concha L et al[52] in 2010 with 11 medically intractable TLE patients with and without hippocampal sclerosis, found positive correlation between diffusivity of fimbria - fornix and histology. Wheareas Thivard et al[63] did not find

significant values in bilateral fornices. Ipsilateral fornix DTI alterations might be secondary to degeneration of mesial temporal efferent fibers (concha et al 2010). Fornix is the limbic component which is closest to csf which might have lead to contamination causing insignificant FA values alteration compared to controls.

The **Cingulum** in our study group showed significantly altered DTI values in posterior cingulum but not in anterior cingulate gyrus. The posterior cingulate showed significant side-to-side difference in patients FA as well as MD compared to controls, with ipsilateral FA of cases showing trend towards significance than controls. A study by Ahmadi et al[10] and Thivard et al[63] also showed decreased FA in ipsilateral cingulate gyrus relative to controls. Whereas, Nilsson et al[64] in 2008 reported increased MD with normal FA in cingulate gyrus of 8 children with TLE which is not in concurrence with our result. This can be due to differences in white matter tissue characteristics in TLE at earlier stages of disease in Nilsson et al patient group.

Yu-Hsuan A Chang et al[55] also showed microstructural changes in frontal and temporolimbic white matter including posterior cingulate and further showed correlation of posterior cingulate with verbal memory in TLE patients. Although we did not test for memory functions, posterior cingulate involvement is in line with our results.

Extratemporal grey matter of patients and controls:

We analysed the FA and MD values of bilateral **thalami**, **caudate** nucleus of all our 16 patients and compared them with 14 controls.

We observed significantly increased MD and decreased FA in ipsilateral thalamus compared to contralateral side within patients which is similar to result in study by Yin et al[61]. Also ipsilateral thalamus FA is reduced compared to controls. Side-to-side difference of FA and MD in patients is increased compared to controls although ADC did not reach statistical significance. DTI values in caudate did not differ significantly from controls or except for contralateral MD. Ahmadi et al[10] found strong

trend ($p<0.05$) of decreased FA in ipsilateral anterior thalamic radiation compared to controls but not on contralateral side which is similar to our study result.

Bernhardt et al[65] in 2012 demonstrated ipsilateral thalamic atrophy in patients with unilateral TLE, which intensified with longer duration of epilepsy and was more severe in patients with a history of febrile convulsions. using surface-based analysis framework.

Also multiple previous studies have suggested that medial thalamic nuclei are involved in limbic seizure circuitry, particularly in relation to spread to the neocortex. The spinal-limbic pathway which is second most dominant pathway of hippocampal connections after ILF, is dominated by ipsilateral hippocampal-thalamic tracks (20%) as demonstrated by Maller Jerome J et al[66]. in their study on hippocampal connectome using super-resolution 1150- direction diffusion MRI. This can be the reason for DTI changes in ipsilateral thalamus of our TLE patients.

C.Chen et al[54] showed that TLE patients with GTCS had lower FA and higher MD than controls in ipsilateral hippocampal-thalamic pathway (HTP) and those without GTCS had higher MD in HTP compared to controls and concluded that thalamus is important in seizure generalization in TLE. These results are in concurrence with our study results showing altered FA and MD in ipsilateral thalamus.

Extratemporal and Temporal White matter changes of patients and controls:

Though the seizure onset is located within the temporal lobe, through the widespread interaction between cortical and subcortical structures, the epileptic circuitry is widened. We observed widespread DTI abnormalities in extratemporal white matter tracts which were predominantly significant on ipsilateral side to TLE. We studied the DTI parameters in **optic radiation, external capsule, uncinate fasciculus(UF), arcuate fasciculus, superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), inferior fronto-occipital fasciculus(IFO).**

In our study, compared to controls patients showed significant side-to-side difference of FA and MD in external capsule, uncinate fasciculus, arcuate fasciculus and ILF.

Compared to controls, patients showed significantly decreased FA in ipsilateral external capsule, uncinate fasciculus, arcuate fasciculus, inferior longitudinal fasciculus (ILF) and significantly increased MD in ipsilateral external capsule, with a trend towards increased MD in uncinate fasciculus, arcuate fasciculus, inferior longitudinal fasciculus.

Among our patient group, compared to contralateral side, ipsilateral side showed significantly decreased FA in external capsule, optic radiation, uncinate fasciculus, SLF, ILF, IFO and increased MD in external capsule, optic radiation, uncinate fasciculus, SLF, ILF.

Our study results of decreased FA and increased ADC in white matter tracts like uncinate fasciculus, ILF, arcuate fasciculus are in line with findings of study by Bernasconi et al[67] in their voxel-based study of TLE patients. They found ipsilateral white matter reduction in temporal lobe and ipsilateral gray matter reduction in medial and orbitofrontal cortices. The preponderance of GM decrease in the temporo-limbic and prefrontal areas may reflect loss of white matter projections from the primary epileptogenic areas in the mesial temporal lobe to the frontal lobe. White matter tracts originating from the temporopolar, entorhinal, and perirhinal cortices form the arcuate fasciculus and uncinate fasciculus, an association bundle containing the efferent projections of these cortices and the hippocampus to the frontal lobe.

Thivard et al[63] in their study also reported ipsilateral significant DTI changes in temporal and extratemporal white matter. Increased MD was seen in ipsilateral temporal lobe white matter with decreased MD on contralateral side. They also reported decreased FA in ipsilateral white matter of temporal lobe along temporal stem, temporo-occipital junction

and along arcuate fasciculus involving frontal and parietal region which concur with our results of ipsilateral white matter changes.

Our study results of decreased FA and increased ADC on ipsilateral side in uncinate fasciculus, fornix, ILF are in line with, Riley, Jeffrey D et al[58]. In their study of white matter integrity in TLE using tract-based spatial statistics (TBSS) showed and probabilistic tractography, they showed significant FA changes predominantly in ipsilateral hemisphere in 4 clusters: anterior temporal lobe (uncinate fasciculus and ILF), posterior temporal cluster (fornix, ILF) along with increased MD in anterior temporal cluster (uncinate fasciculus, ILF). Mean FA was also positively correlated with delayed memory in their study, whereas we did not test for memory function correlations in our study.

Our results of uncinate and arcuate fasciculus are also in concurrence with that of study by Lin et al[56], which showed that TLE patients had decreased FA and increased MD ipsilateral to seizure onset when compared to controls.

The fact that reduced FA and increased MD in SLF, Uncinate fasciculus, Arcuate fasciculus is isolated to the side seizure focus in our study supports the involvement of frontal-temporal tract in the epileptogenic network of TLE.

Multiple studies demonstrated correlation of DTI changes in temporal and extratemporal white matter with cognitive, memory, executive functions and language functions (Shaimaa H Soliman et al[60], Mcdonald et al[68] 2008, Diehl et al[59] 2008). Though we did not test the cognitive profiles of our patient group, it is an area of further research in these areas.

We did not find any significant changes compared to controls in **optic radiation, SLF, IFO** which differ from results of study by Ahmadi et al[10] where they found widespread reductions in fiber tract FA in TLE patients although they were more pronounced ipsilateral to the seizure focus. TLE patients in their study showed decreased FA in the ipsilateral

IFOF ($p<0.01$), and SLF ($p<0.005$). This difference might be due various reasons. Mean age (37 vs 29 years) and duration (23years vs 16 years) in their TLE patient group was higher compared to our patient group. Another reason can be due to different methodologies used for DTI analysis.In their study, fiber tract FAs were calculated using DTI Studio's algorithm which essentially performs a weighted average of all voxels within the fiber tract of interest. In our study we performed probabilistic atlas based maps using MATLAB and SPM software.

Our study did not show significant DTI changes in contralateral side to hippocampal sclerosis. However, some studies reported significant changes in bilateral hemispheres in TLE patients[10]. Diogo Goulart Corrêa et al[69] (2018) conducted a study to evaluate white matter (WM) integrity in vivo in patients with unilateral mesial temporal sclerosis (MTS). Compared with the control groups, patients with MTS had decreased FA affecting widespread WM tracts as well as extensive areas with increased RD, bilaterally and independent of the disease side. Areas with decreased FA and increased RD overlapped substantially. The study concluded that diffusion tensor imaging abnormalities were observed within and beyond the temporal lobe in patients with MTS. Patients with R- and L-MTS had extensive bilateral abnormalities in comparison to controls. These study results differ from our study results which showed predominantly ipsilateral changes in WM tracts. This might be due to different mean duration of epilepsy between studies, or different methodologies adapted for DTI imaging analysis, number of directions in which DTI scan was done, variations in the amount of each anatomical region included in the ROI.

Diogo Goulart correa et al performed Tract-based spatial statistics (TBSS) analysis, where as we performed probabilistic atlas maps based method in our study.

Gross et al[16], in their meta-analysis of 10 studies observed that though the cause and implications of white matter changes are unclear, they represent downstream axonal degeneration secondary to spreading

seizure activity. They also observed that the changes are variable between studies in grey and white matter tract involvement and represent variations in patient selection, methodology, duration and propagation of seizure activity.

LIMITATIONS OF OUR STUDY

1. Sample size of subjects (cases and controls) was less in our study.
2. We used probabilistic diffusion tensor atlas for ROIs rather than manually placed ROIs, which might affect the fractional anisotropy and mean diffusivity when compared to studies using manually placed ROIs.
3. We used EEG and MRI epilepsy protocol findings to lateralise the lesion in cases, whereas some other studies confirmed lateralization by correlating with post-surgical outcome.
4. Although the DTI scan was done atleast a week after seizure occurrence, subclinical seizures, not identified, if present in patients could have an impact on our study values.
5. In our study, we have done diffusion tensor imaging in 32 non collinear directions. Yield of the study might increase with further increase in number of directions.
6. We did not include age of onset or duration and seizure frequency as variables in our analysis. These may effect the fractional anisotropy and mean diffusivity.

Recommendations for further research

1. Diffusion tensor imaging might be incorporated in epilepsy protocol as asymmetrically altered FA and ADC values can be a useful clue in lateralization of seizure focus in equivocal cases as there is predominantly ipsilateral alterations in the FA and ADC values.
2. Increasing the number of directions, instead of 32, might yield better results.
3. Cognition tests like episodic memory, language, executive functions can be correlated with DTI changes as it might help in planning for

surgery and prognostication also by understanding their impact on outcome of surgery.

Summary & Conclusion

- The objective of this study was to study the role of Diffusion Tensor Imaging (DTI) in Temporal lobe epilepsy patients.
- It was a prospective observational study done with total of 30 subjects among which 16 were cases with unilateral TLE and 14 were healthy controls.
- Mean age of cases was 29 years (±9 years) and mean age of controls is 33(±9 years).
- Among cases, majority (63.0%) were males (n=10) and 37.0% were females (n=6), whereas in control group males(n=7) and females (n=7) constituted 50% each.
- The disease duration varied from 4 years to 40 years with mean duration of 16years (±9years).
- When compared to controls, patients had significantly ($p<0.05$) decreased mean FA on ipsilateral side to seizure focus in parahippocampal gyrus, thalamus, external capsule, uncinate fasciculus, arcuate fasciculus, inferior longitudinal fasciculus whereas in ipsilateral hippocampus ($p=0.127$) and posterior cingulate gyrus (0.110) FA showed trend towards significance.
- When compared to controls, patients had significantly ($p<0.05$) increased ADC on ipsilateral side to seizure focus in hippocampus, parahippocampal gyrus, external capsule, fornix, whereas in ipsilateral uncinate fasciculus (0.076), arcuate fasciculus (0.068) and in inferior longitudinal fasciculus (0.055) ADC showed trend towards significance.
- Compared to controls only 2 areas in patients showed altered DTI values on the contralateral side of seizure focus. FA was significantly decreased in the contralateral caudate (0.047). ADC of fornix (0.057) on the contralateral side in patient group showed trend towards significance.

- We further compared the mean of side-to-side differences of FA and ADC between cases and controls. Cases had significantly higher mean of side-to-side difference of FA and ADC in hippocampus, parahippocampal gyrus, external capsule, posterior cingulate gyrus, uncinate fasciculus, arcuate fasciculus, and inferior longitudinal fasciculus. Whereas thalamus and fornix showed higher mean of side-to-side difference of FA only but not of ADC values.
- However caudate nucleaus, anterior cingulate gyrus, optic radiation, superior longitudinal fasciculus, inferior fronto-occipital fasciculus did not show significant changes in FA or ADC when compared to controls.
- Among cases group, when compared to contralateral side, ipsilateral side had significantly ($p<0.05$) decreased mean FA and increased ADC in hippocampus, PHG, thalamus, external capsule, PCG, optic radiation, fornix, uncinate fasciculus, SLF and ILF, whereas arcuate fasciculus and IFO showed decreased FA and ACG showed increased ADC.
- Our study showed that, DTI values of fractional anisotropy (FA) and mean diffusivity (MD) were altered significantly ($p<0.05$) in temporal as well as extratemporal regions of TLE patients, and these were noted predominantly on the side ipsilateral to seizure focus (EEG and MRI).

Conclusion

This study suggests that diffusion tensor imaging may reveal abnormalities in patients with TLE. These changes are not necessarily restricted to the pathological hippocampus and involve a larger network in temporal lobes and extratemporal brain regions as well. This pattern might reflect indirectly the epileptogenic network. These changes were observed predominantly on the ipsilateral side of seizure focus in our study. Altered DTI values (FA and ADC) can be a useful tool in addition to conventional MRI and EEG in lateralizing the seizure focus in

equivocal cases and in cases with normal conventional MRI which might help pre-surgical evaluation and planning for surgery. Further studies are needed with larger sample size and improved spatial resolution to delineate the role of DTI in understanding the pathophysiology of TLE as well as cognitive and clinical outcomes in TLE patients.

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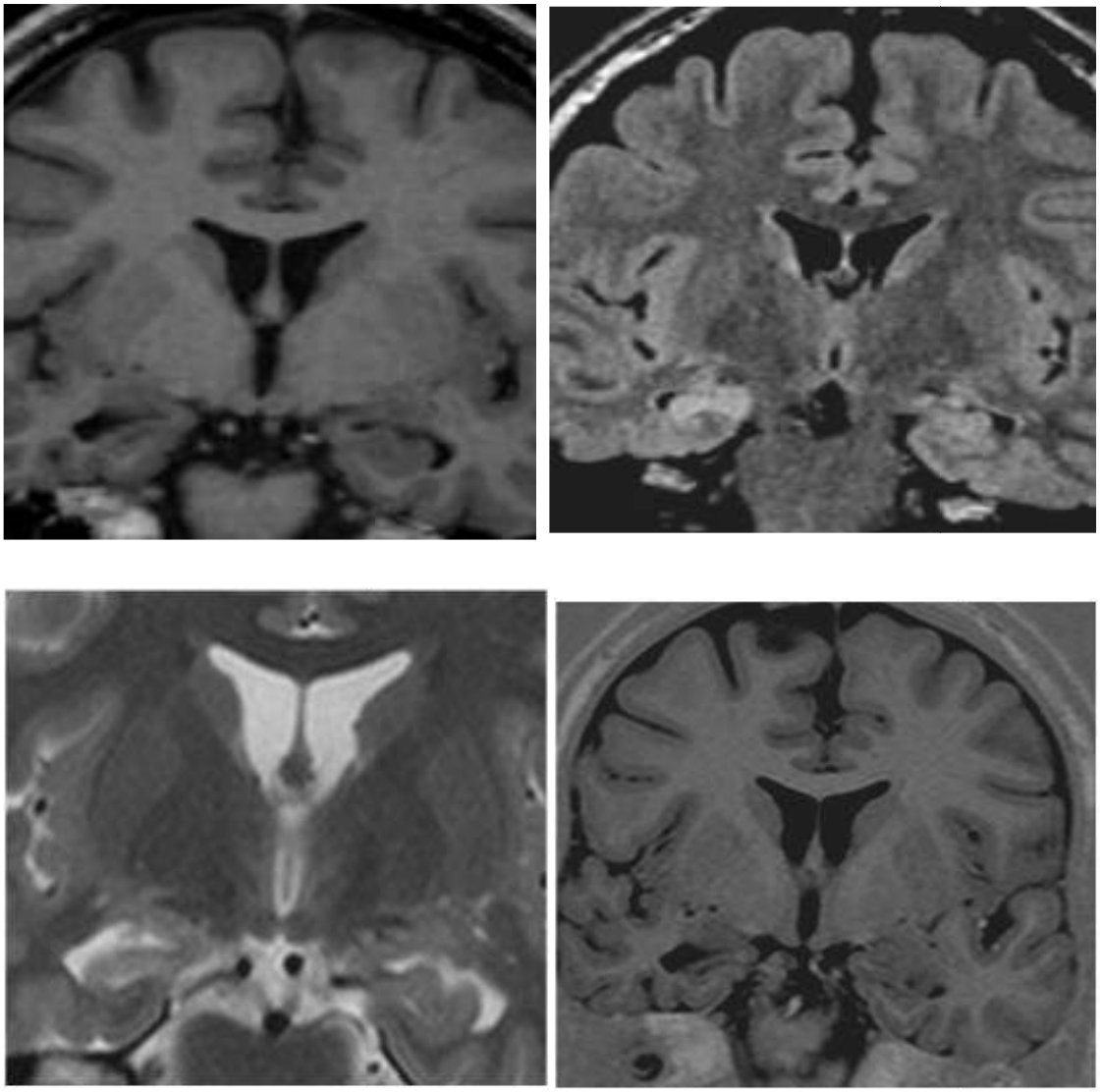
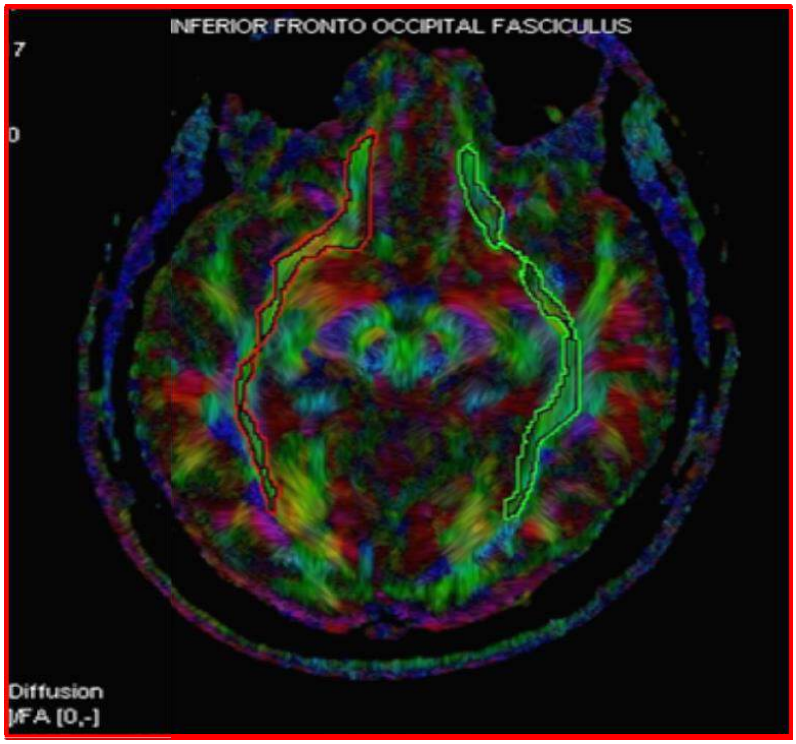
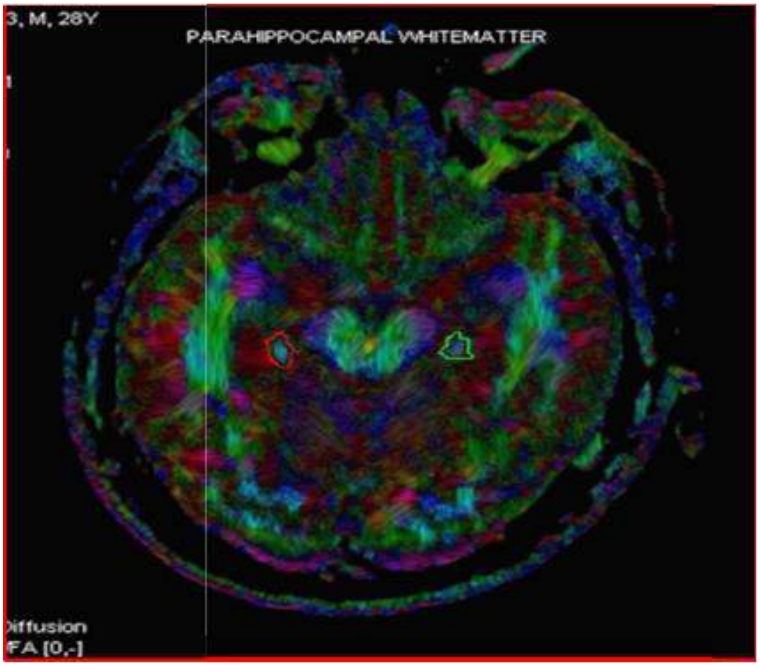


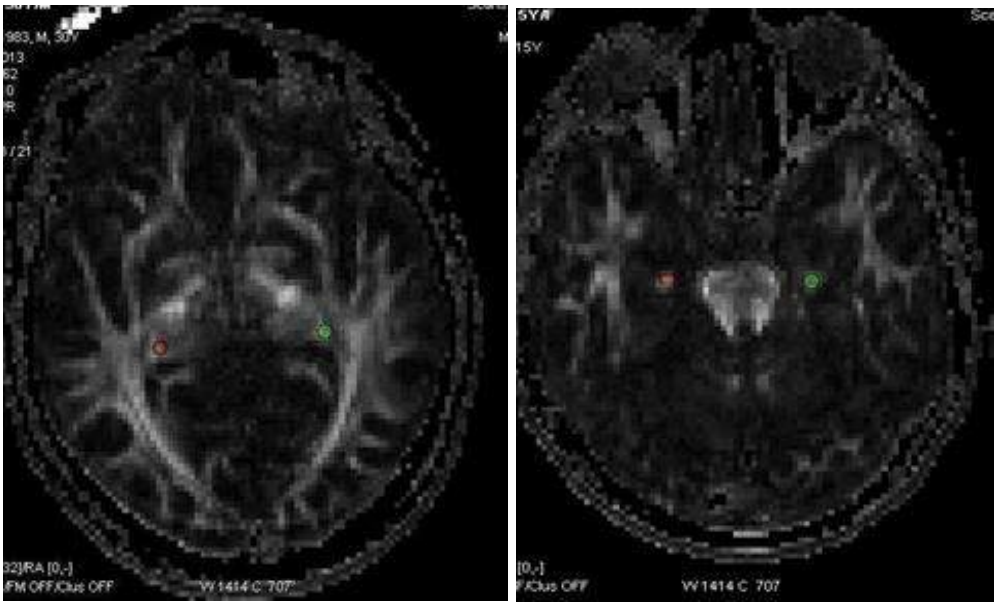
Picture 1. Cases with right mesial temporal lobe sclerosis on MRI epilepsy protocol



Picture 2. Region of interest in inferior fronto-occipital longitudinal fasciculus along with Diffusion Tensor Imaging (DTI) measurements.



Picture 3. Region of interest in bilateral parahippocampus



Picture 4. Region of interest in fornix and parahippocampus

S.No.	MRD	Name	Age (Years)	Handedness	Sex	Duration of Epilepsy	Semiology	EEG focus
1	514599	P	21	Right	F	8years	Behavioural arrest with oral & right hand automatisms with ictal speech, GTCS	Right Temporal Lobe
2	783226	SS	34	Right	M	18years	feeling of dizziness f/b behavioural arrest, GTCS	Right Temporal Lobe
3	958797	MS	34	Right	M	6years	Behavioural arrest with post-ictal nose wipe with left hand, GTCS	Left Temporal lobe
4	899380	GR	20	Right	F	15years	Headache with vertigo/dizziness f/b behavioural arrest	Right Temporal Lobe
5	183447	A	16	Right	M	4years	Behavioural arrest	Left Temporal lobe
6	313648	JS	28	Left	M	18years	Behavioural arrest with bimanual automatism with post-ictal aphasia, GTCS	Left Temporal lobe
7	337781	AK	21	Right	F	15years	Focal seizures with lip smacking with right hand dystonic posturing with secondary GTCS	Left Temporal lobe
8	938609	GS	26	Right	M	24years	Feeling of fear, vertigo f/b behavioural arrest with falls bimanual automatism	Left Temporal lobe
9	1010054	JS	21	Right	M	10years	Behavioural arrest with dystonic posturing	Right Temporal Lobe
10	540162	JK	21	Right	F	10years	Behavioural arrest	Right Temporal Lobe
11	614192	KS	30	Right	M	12years	Palpitations, Behavioural arrest	Right Temporal Lobe
12	32861	MG	42	Right	M	28years	Behavioural arrest with orofacial automatisms	Left Temporal lobe
13	964356	RS	31	Right	M	17years	Focal seizures with lip smacking with left hand dystonic posturing	Right Temporal Lobe
14	635090	MK	28	Right	F	7years	Behavioural Arrest with palpitation, GTCS	Left Temporal lobe
15	855419	N	38	Right	F	21years	Olfactory aura, Behavioural arrest with oroalimentary Automatism, GTCS	Right Temporal Lobe
16	731748	GS	48	Right	M	40years	Behavioural arrest with Right hand automatism, GTCS	Left Temporal lobe

S.No.	MRD	MRI (EP)	Fractional Anisotropy (FA)																							
			Hippocampus		PHG		Caudate		Thalamus		External capsule		ACG		PCG		Optic Radiation		Fornix		Uncinate Fasciculus		Arcuate fasciculus		SLF	
			C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L
1	514599	Right Hippocampal sclerosis	0.18	0.16	0.17	0.14	0.14	0.15	0.27	0.25	0.28	0.26	0.13	0.11	0.15	0.13	0.44	0.42	0.18	0.16	0.24	0.19	0.22	0.17	0.2	0.19
2	783226	Right Hippocampal sclerosis	0.2	0.17	0.13	0.12	0.15	0.15	0.27	0.26	0.35	0.31	0.11	0.11	0.14	0.12	0.36	0.32	0.22	0.21	0.19	0.18	0.25	0.19	0.22	0.17
3	958797	Normal	0.17	0.15	0.15	0.14	0.16	0.16	0.31	0.29	0.29	0.24	0.12	0.11	0.13	0.12	0.37	0.38	0.2	0.18	0.2	0.18	0.21	0.18	0.17	0.16
4	899380	Right Hippocampal sclerosis	0.19	0.17	0.18	0.15	0.13	0.14	0.27	0.25	0.29	0.25	0.13	0.12	0.17	0.15	0.44	0.41	0.18	0.16	0.22	0.19	0.24	0.18	0.19	0.18
5	183447	Left Hippocampal sclerosis	0.16	0.14	0.14	0.12	0.15	0.14	0.29	0.26	0.25	0.25	0.12	0.12	0.15	0.14	0.4	0.38	0.15	0.14	0.17	0.18	0.21	0.21	0.2	0.19
6	313648	Left Hippocampal sclerosis	0.2	0.18	0.17	0.15	0.17	0.17	0.3	0.27	0.29	0.3	0.14	0.14	0.18	0.14	0.39	0.4	0.23	0.21	0.28	0.26	0.23	0.18	0.23	0.22
7	337781	Left Hippocampal sclerosis	0.17	0.14	0.16	0.13	0.16	0.16	0.28	0.25	0.28	0.24	0.14	0.13	0.16	0.13	0.38	0.36	0.22	0.2	0.19	0.17	0.22	0.19	0.21	0.19
8	938609	Left Hippocampal sclerosis	0.17	0.15	0.14	0.13	0.13	0.13	0.3	0.28	0.24	0.25	0.13	0.13	0.15	0.15	0.44	0.42	0.18	0.16	0.19	0.18	0.21	0.17	0.22	0.2
9	1010054	Right Hippocampal sclerosis	0.2	0.17	0.15	0.13	0.14	0.15	0.29	0.29	0.25	0.21	0.12	0.14	0.14	0.14	0.36	0.35	0.31	0.26	0.22	0.18	0.21	0.18	0.2	0.18
10	540162	Right Hippocampal sclerosis	0.19	0.16	0.17	0.15	0.14	0.15	0.29	0.26	0.28	0.24	0.14	0.13	0.18	0.16	0.37	0.35	0.24	0.22	0.25	0.2	0.22	0.2	0.22	0.19
11	614192	Right Hippocampal sclerosis	0.16	0.15	0.18	0.16	0.15	0.19	0.27	0.25	0.34	0.27	0.13	0.1	0.15	0.15	0.38	0.38	0.22	0.21	0.21	0.19	0.31	0.23	0.32	0.28
12	32861	Left Hippocampal sclerosis	0.16	0.14	0.19	0.16	0.13	0.15	0.29	0.27	0.31	0.29	0.12	0.15	0.13	0.12	0.41	0.41	0.22	0.21	0.23	0.21	0.2	0.17	0.22	0.23
13	964356	Right Hippocampal sclerosis	0.16	0.14	0.17	0.16	0.12	0.1	0.26	0.26	0.31	0.25	0.14	0.12	0.17	0.15	0.37	0.32	0.18	0.13	0.25	0.21	0.23	0.21	0.25	0.21
14	635090	Normal	0.18	0.15	0.18	0.15	0.18	0.16	0.29	0.29	0.35	0.3	0.13	0.15	0.16	0.17	0.37	0.37	0.23	0.18	0.22	0.2	0.25	0.2	0.27	0.22
15	855419	Right Hippocampal sclerosis	0.19	0.16	0.2	0.18	0.23	0.19	0.33	0.31	0.34	0.26	0.17	0.15	0.2	0.18	0.34	0.33	0.26	0.26	0.21	0.22	0.21	0.18	0.26	0.25
16	731748	Left Hippocampal sclerosis	0.16	0.14	0.13	0.12	0.14	0.14	0.3	0.29	0.33	0.27	0.12	0.11	0.13	0.12	0.4	0.31	0.23	0.2	0.19	0.18	0.25	0.19	0.25	0.24

S.No.	MRD	Apparent Diffusion Coefficient (ADC)																													
		ILF		IFO		Hippocampus		PHG		Caudate		Thalamus		External Capsule		ACG		PCG		Optic Radiation		Fornix		Uncinate Fasciculus		Arcuate Fasciculus		SLF		ILF		IFO	
		C/L	I/L	C/L	I/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L
1	514599	0.28	0.22	0.27	0.29	1.18	1.17	1.62	1.43	0.91	0.91	0.96	0.95	1.05	0.99	1.03	0.99	1.12	1.02	0.9	0.86	2.34	2.1	1.23	1.11	1.02	0.89	1.03	1.01	0.96	0.91	1.06	1.04
2	783226	0.32	0.24	0.26	0.24	1.24	1.19	1.57	1.57	0.89	0.85	1.19	1.16	1.09	0.95	1.03	1.02	1.16	1.14	1.03	0.99	1.68	1.66	1.24	1.2	0.99	0.88	1.17	0.93	0.94	0.9	1.13	1.09
3	958797	0.32	0.27	0.25	0.24	1.04	1.01	1.42	1.35	1.1	1.2	0.97	0.96	1.06	1.03	1.16	1.09	1.11	1.07	0.83	0.79	1.9	1.83	1.12	0.98	0.95	1.06	1.14	1.15	0.92	0.85	0.87	1.03
4	899380	0.31	0.23	0.27	0.26	1.34	1.01	1.37	1.1	0.99	0.98	1.15	1.05	1.01	0.98	1.04	1.01	1.14	0.99	0.91	0.9	1.57	1.43	1.19	1.11	1.01	0.96	0.95	0.93	0.96	0.85	0.91	0.93
5	183447	0.29	0.26	0.3	0.3	1.3	1.12	1.4	1.34	1.1	1.08	1.12	1.13	1.01	0.99	0.96	0.97	1.01	0.98	0.91	0.86	2.72	2.45	0.99	0.98	0.89	0.89	0.94	0.95	0.9	0.87	0.89	0.89
6	313648	0.3	0.28	0.28	0.26	1.26	0.96	1.4	1.24	0.91	0.91	0.98	0.94	0.93	0.87	0.9	0.9	1.03	0.91	0.91	0.87	1.9	2.1	0.96	0.92	0.91	0.89	1.04	0.95	0.85	0.81	0.87	0.9
7	337781	0.31	0.25	0.25	0.23	1.01	0.98	1.57	1.42	1.2	1.1	1.21	1.04	1.03	0.96	1.36	1.01	1.16	1.1	0.96	0.91	1.41	1.34	1.21	1.11	1.02	0.92	0.97	0.94	0.97	0.9	0.98	0.95
8	938609	0.34	0.3	0.27	0.27	1.35	1.09	1.32	1.21	0.98	1.01	0.97	0.96	1.11	1.05	0.98	0.97	1.02	0.96	0.88	0.84	2.2	2.16	1.02	1	0.95	0.92	1.01	0.93	0.86	0.81	0.87	0.91
9	1010054	0.27	0.21	0.28	0.24	1.24	1.08	1.52	1.43	0.82	0.79	0.96	0.89	1.08	1.02	0.94	1.01	1.11	1.07	0.9	0.91	1.55	1.5	1.04	1.01	0.96	0.95	1.02	0.97	0.91	0.89	0.94	0.9
10	540162	0.28	0.21	0.27	0.22	1.26	1.11	1.4	1.21	0.91	0.91	0.99	0.94	1.01	0.99	1.05	0.99	1.15	0.99	0.97	0.95	1.76	1.57	1.14	1.02	0.94	0.88	1.04	0.96	0.99	0.92	1.02	0.99
11	614192	0.33	0.24	0.29	0.28	1.31	1.17	1.51	1.46	0.95	1.06	1.08	1.06	1.07	0.93	1.16	1.04	1.14	1.08	1.01	1.04	1.9	1.74	1.08	1.03	0.87	0.85	0.87	0.84	0.92	0.87	0.99	0.97
12	32861	0.25	0.22	0.26	0.24	1.38	1.21	1.38	1.33	1.42	1.5	1.07	1.05	1.01	0.93	1.01	1.04	1.05	1.04	0.86	0.81	2.03	2.01	1.09	1.01	0.97	0.96	1	0.97	0.89	0.81	0.99	0.96
13	964356	0.29	0.24	0.29	0.27	1.51	1.28	1.23	1.2	2.01	1.88	1.22	1.17	1.06	1.03	1.08	0.95	1.13	1.04	1.02	0.95	2.68	2.27	0.96	0.94	0.99	0.95	1.09	0.98	0.91	0.86	0.99	0.96
14	635090	0.23	0.18	0.27	0.25	1.04	1.01	1.2	0.89	1.06	0.97	1.09	1.05	0.85	0.8	0.87	0.9	0.94	0.93	1.16	0.91	1.28	1.21	1.2	1.04	1.01	0.96	0.98	0.96	0.91	0.87	1.18	1.23
15	855419	0.29	0.22	0.26	0.25	0.92	0.92	1.4	1.12	0.67	0.64	0.85	0.79	0.77	0.78	0.81	0.74	0.24	0.21	0.85	0.81	1.23	0.9	1.03	1.02	0.99	0.84	0.91	0.89	0.85	0.79	1.1	0.96
16	731748	0.28	0.21	0.25	0.26	1.2	1.01	1.72	1.55	1.2	1.1	1.07	1.02	1.01	0.96	1.22	1.07	1.14	1.04	1.12	0.99	1.56	1.44	1.16	1.02	0.94	0.9	0.98	0.99	0.93	0.88	1.01	0.99

S.No.	MRD	Name	Age (Years)	Handedness	Sex	Duration of Epilepsy	Semiology	EEG focus	MRI (EP)	Fractional Anisotropy (FA)															
										Hippocampus		PHG		Caudate		Thalamus		External capsule		ACG		PCG		Optic Radiation		Fornix	
										C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L
1	453737	HK	25	Right	F	-	-	-	Normal study	0.17	0.16	0.16	0.16	0.16	0.15	0.3	0.28	0.3	0.29	0.14	0.14	0.14	0.14	0.39	0.38	0.27	0.26
2	796203	LS	29	Right	M	-	-	-	Normal study	0.16	0.16	0.16	0.15	0.14	0.12	0.3	0.28	0.3	0.3	0.15	0.15	0.14	0.14	0.41	0.4	0.25	0.24
3	981447	NS	28	Right	M	-	-	-	Normal study	0.18	0.16	0.16	0.15	0.2	0.19	0.31	0.3	0.33	0.32	0.13	0.13	0.16	0.15	0.43	0.4	0.22	0.2
4	988056	SR	30	Right	M	-	-	-	Normal study	0.19	0.18	0.19	0.18	0.16	0.16	0.34	0.34	0.27	0.26	0.15	0.14	0.17	0.16	0.4	0.39	0.18	0.18
5	1006064	KK	52	Left	M	-	-	-	Normal study	0.16	0.15	0.17	0.15	0.16	0.16	0.28	0.28	0.3	0.29	0.14	0.13	0.16	0.16	0.48	0.38	0.19	0.17
6	1012357	GB	36	Right	F	-	-	-	Normal study	0.2	0.18	0.19	0.18	0.16	0.15	0.28	0.27	0.26	0.25	0.15	0.15	0.18	0.17	0.32	0.28	0.24	0.23
7	514466	KK	39	Right	F	-	-	-	Normal study	0.16	0.15	0.19	0.18	0.17	0.16	0.29	0.29	0.33	0.31	0.12	0.12	0.16	0.15	0.36	0.34	0.2	0.18
8	884111	RA	34	Left	M	-	-	-	Normal study	0.2	0.19	0.17	0.16	0.16	0.16	0.3	0.3	0.36	0.35	0.14	0.14	0.15	0.14	0.4	0.39	0.24	0.23
9	442277	BK	22	Right	F	-	-	-	Normal study	0.15	0.14	0.18	0.17	0.18	0.17	0.29	0.28	0.34	0.32	0.13	0.13	0.17	0.17	0.38	0.36	0.21	0.19
10	464886	SK	45	Left	F	-	-	-	Normal study	0.16	0.15	0.16	0.15	0.18	0.18	0.3	0.28	0.33	0.32	0.14	0.13	0.15	0.15	0.4	0.37	0.2	0.19
11	1013942	RS	42	Right	M	-	-	-	Normal study	0.2	0.19	0.16	0.16	0.18	0.17	0.33	0.33	0.29	0.27	0.12	0.12	0.13	0.13	0.44	0.4	0.27	0.26
12	1014002	GD	32	Right	M	-	-	-	Normal study	0.17	0.17	0.16	0.16	0.18	0.17	0.28	0.28	0.32	0.3	0.14	0.13	0.19	0.18	0.44	0.43	0.23	0.22
13	1013901	GG	17	Right	F	-	-	-	Normal study	0.15	0.15	0.16	0.15	0.15	0.15	0.26	0.25	0.29	0.27	0.13	0.11	0.14	0.13	0.39	0.36	0.2	0.18
14	1010488	S	35	Right	F	-	-	-	Normal study	0.15	0.15	0.16	0.15	0.17	0.16	0.3	0.29	0.24	0.24	0.13	0.13	0.16	0.16	0.41	0.37	0.18	0.18

		Apparent Diffusion Coefficient (ADC)																																	
		Uncinate Fasciculus		Arcuate fasciculus		SLF		ILF		IFO		Hippocampus		PHG		Caudate		Thalamus		External Capsule		ACG		PCG		Optic Radiation		Fornix		Uncinate Fasciculus		Arcuate Fasciculus		SLF		ILF		IFO	
S.No.	MRD	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L
1	453737	0.2	0.19	0.23	0.21	0.2	0.2	0.32	0.27	0.28	0.27	1.01	0.98	1.25	1.18	0.86	0.85	0.91	0.9	0.92	0.91	0.92	0.92	0.91	0.91	0.85	0.82	1.38	1.28	1	0.9	0.91	0.9	1.04	0.99	0.86	0.86	0.98	0.97
2	796203	0.25	0.24	0.28	0.28	0.27	0.26	0.35	0.3	0.32	0.29	1.19	1.13	1.28	1.17	1.49	1.46	1.07	0.99	0.94	0.91	0.97	0.92	0.97	0.95	0.9	0.88	1.52	1.46	0.92	0.91	0.84	0.84	0.86	0.85	0.85	0.84	0.87	0.85
3	981447	0.23	0.21	0.3	0.28	0.29	0.23	0.32	0.31	0.31	0.28	1.02	0.97	1.42	1.32	0.89	0.86	1.06	1.02	0.94	0.9	1.02	0.97	1.03	0.98	1.03	0.93	1.61	1.55	1	0.97	0.93	0.92	0.92	0.86	0.85	0.85	0.97	0.93
4	988056	0.25	0.24	0.22	0.21	0.22	0.19	0.28	0.26	0.29	0.27	0.97	0.96	1.12	1.1	0.91	0.9	0.84	0.84	0.93	0.89	0.93	0.9	0.91	0.9	0.83	0.8	1.56	1.56	0.91	0.91	0.89	0.88	0.92	0.91	0.83	0.83	0.82	0.81
5	1006064	0.24	0.23	0.29	0.28	0.26	0.24	0.33	0.31	0.33	0.29	1.24	1.13	1.37	1.3	1.1	1.06	1.21	1.21	1.01	0.96	1.08	1.05	1.07	1.03	1.22	0.98	2.3	1.99	1.03	1.03	0.84	0.83	1	0.92	0.9	0.87	1.02	0.99
6	1012357	0.24	0.24	0.21	0.18	0.19	0.19	0.25	0.22	0.28	0.25	1.2	1.05	1.13	1.03	1.13	1.1	1.1	1.06	1.02	0.99	0.94	0.88	0.94	0.94	0.93	0.92	2.04	1.85	1.01	0.98	0.98	0.96	1.03	1.02	0.96	0.92	1.01	0.94
7	514466	0.21	0.2	0.26	0.23	0.24	0.23	0.3	0.27	0.27	0.26	1.02	1.01	1.28	1.22	0.83	0.83	0.94	0.93	0.91	0.89	0.99	0.96	1.03	1.01	0.93	0.88	1.23	1.07	1.18	1.17	0.89	0.87	0.91	0.9	0.9	0.87	1.07	1.06
8	884111	0.23	0.22	0.26	0.26	0.26	0.23	0.33	0.28	0.28	0.27	1.08	1.03	1.26	1.22	0.88	0.85	0.96	0.95	0.87	0.85	1.01	0.97	1.01	0.98	0.98	0.96	1.51	1.5	1.01	0.99	0.87	0.86	0.91	0.88	0.85	0.85	1.02	0.98
9	442277	0.22	0.2	0.19	0.19	0.21	0.21	0.19	0.19	0.25	0.25	1.13	1.11	1.4	1.4	0.99	0.98	1.04	1.03	0.87	0.87	1.11	1.02	1.04	0.99	1.02	1.01	1.19	1.18	1.07	1.06	1.01	1.01	1.06	0.99	0.86	0.85	1.12	1.1
10	464886	0.19	0.19	0.21	0.19	0.22	0.22	0.26	0.24	0.24	0.22	1.24	1.18	1.41	1.3	1.42	1.4	1.15	1.11	0.89	0.88	1.13	1.05	1.19	1.18	1.02	0.99	1.15	1.06	1.14	1.13	1	0.99	1.1	1.05	0.93	0.91	0.99	0.98
11	1013942	0.23	0.21	0.2	0.17	0.19	0.19	0.23	0.22	0.28	0.26	1.02	0.99	1.35	1.35	0.8	0.79	0.85	0.82	0.88	0.85	1.01	0.98	1.04	0.99	0.91	0.88	1.16	1.11	1.05	1.04	0.98	0.96	1.09	1.01	0.88	0.85	1.06	1.05
12	1014002	0.22	0.21	0.24	0.22	0.24	0.21	0.34	0.31	0.27	0.26	1.2	1.15	1.32	1.23	1.13	1.1	1.13	1.1	0.96	0.92	0.99	0.95	0.95	0.93	0.84	0.82	1.42	1.36	1.2	1.19	0.99	0.99	1.01	0.96	0.91	0.89	1.03	1.02
13	1013901	0.26	0.24	0.25	0.24	0.2	0.19	0.31	0.26	0.28	0.28	1.15	1.12	1.42	1.37	1.06	1.04	1.19	1.18	1.04	1.01	1.16	1.09	1.09	1.09	0.93	0.92	2.13	2.09	0.97	0.96	0.97	0.96	1.2	1.11	0.96	0.94	0.95	0.92
14	1010488	0.21	0.21	0.24	0.23	0.21	0.2	0.31	0.27	0.28	0.26	1.21	1.18	1.31	1.21	1.31	1.29	0.99	0.98	0.91	0.89	0.99	0.96	0.99	0.98	0.85	0.83	1.32	1.27	1.09	1.08	0.86	0.85	0.99	0.93	0.87	0.84	0.99	0.98

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No. BFUHS/2K19p-TH/ 1752

Date 13/5/19

The Principal,
DMC, Ludhiana.

Subject: Approval of Plan of Thesis.

This is to inform you that the Faculty of Medical Sciences in its meeting held on 29.05.2019 has approved the plan of thesis of **Dr. Sajja Venkatesh**, a student of your college for **DM Neurology** along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis

Role of diffusion tensor imaging in mesial temporal lobe epilepsy

Supervisor
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Dept. of Neurology,
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Co-Supervisor
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The student has to submit the four copies of thesis (along with PDF format) , to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She must directed to attach a photocopy of this letter with the forwarding letter while submitting thesis to the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic,(if any).

S P Singh

Dr. S P Singh MS(Oph)
Controller of Examinations

Note :

1. *If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.*
2. *The student may submit the thesis as per the schedule already conveyed i.e for May/June examination 30th Nov of the preceding the year of examination and for Nov/Dec examinations 31st May of the year of examination.*

ROLE OF DIFFUSION TENSOR IMAGING IN MESIAL TEMPORAL LOBE EPILEPSY

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED
IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

DOCTORATE OF MEDICINE

In

Neurology

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES
FARIDKOT

APRIL, 2019

DR SAJJA VENKATESH

DEPARTMENT OF NEUROLOGY
DAYANAND MEDICAL COLLEGE & HOSPITAL, LUDHIANA

ABSTRACT OF PLAN OF THESIS

Title	Role of Diffusion Tensor Imaging in Mesial Temporal Lobe Epilepsy
For the degree of	D.M. Neurology
Name of the candidate	Dr Sajja Venkatesh
Supervisor	Dr. Gagandeep Singh, Professor & Head, Department of Neurology, Dayanand Medical College and Hospital, Ludhiana
Co-supervisor	Dr. Kavita Saggar, Professor & Head, Department of Radiodiagnosis, DMC&H, Ludhiana Dr. Monika Singla, Associate Professor, Department of Neurology, DMC&H, Ludhiana
Institution	Dayanand Medical College & Hospital, Ludhiana
University	Baba Farid University of Health Sciences, Faridkot

Introduction: Diffusion Tensor Imaging (DTI) is a new non invasive MRI technique which provides insight into the white matter microstructure. In focal epilepsy widespread DTI abnormalities have been reported. In mesial temporal lobe sclerosis (MTLS) patients, although conventional MRI only shows unilateral involvement of the hippocampal sclerosis, DTI was found to be useful in evaluating the integrity of white matter tracts of other regions of brain as well.

Aim and Objectives: We aimed to prove this hypothesis by assessing DTI measurements in various portions of the brain in MTLS patients.

Material and methods: We will evaluate patients with MTLS by using DTI, MRI, clinical and EEG parameters. We will compare the mean diffusivity (trace D) and fractional anisotropy (FA) from symmetrical voxels. We will compare these measurements with the EEG, high-resolution MR imaging, and clinical information.

Clinical significance: DTI measurements in an MTLE patient can help in pre surgical evaluation of epilepsy and surgical planning and also adds to the diagnosis in equivocal cases.

Keywords: DTI, MTLE, HS.

(Signature)	(Signature)	(Signature)	(Signature)	(Signature)
Candidate	Co-supervisor	Co-supervisor	Supervisor	Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"ROLE OF DIFFUSION TENSOR IMAGING IN MESIAL TEMPORAL LOBE EPILEPSY"** exist in the Department of Neurology, DMC&H, Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis is genuine and is collected by the candidate himself under our supervision and guidance.

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Date : 27-04-2019

APPROVAL PROFORMA
BY
RESEARCH & ETHICAL COMMITTEE
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Name of candidate	Dr. Sajja Venkatesh
Department	Neurology
Topic of Thesis	Role of Diffusion Tensor Imaging in Mesial Temporal Lobe Epilepsy
Likely date of appearing in PG examination	May 2021
Date of enrollment	27 August, 2018
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1) Supervisor	Dr. Gagandeep Singh
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1. HOD Pharmacology	1. HOD Physiology
2. HOD Surgery	2. HOD Pathology
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5. Dean Academics	5. HOD Medicine
6. Vice Principal	6. HOD Surgery
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	12. Principal

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Research Committee

Approved: Yes / No

Chairperson
Ethics Committee

BABA FARID UNIVERSITY OF HEALTH SCIENCES, FARIDKOT

PROFORMA FOR REGISTRATION OF SUBJECT FOR DISSERTATION

1	NAME OF THE CANDIDATE AND ADDRESS	Dr. Sajja Venkatesh
2	NAME OF THE INSTITUTE	Dayanand Medical College, Ludhiana.
3	COURSE OF STUDY AND SUBJECT	D.M. Neurology
4	DATE OF ADMISSION OF COURSE	27th August 2018
5	TITLE OF THE TOPIC	Role of Diffusion Tensor Imaging in Mesial Temporal Lobe Epilepsy

6 BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy in adulthood.[1]. Among such patients, mesial temporal sclerosis (MTS, also called hippocampal sclerosis) is the most common underlying pathologic abnormality, as has been demonstrated in both autopsy and post resection studies.[2]

Although mesial temporal sclerosis (MTS) has long been recognized in association with temporal lobe epilepsy (TLE), there is a growing body of literature suggesting structural abnormalities extending beyond the temporal lobe in patients with TLE. Diffusion tensor imaging (DTI) is a novel imaging technique that provides insight into the structural integrity of cerebral white matter.[3]

DTI studies have demonstrated extensive bilateral white matter abnormalities in TLE that extend far beyond the temporal lobe, even in patients with unilateral MTS. We would like to study this hypothesis by assessing DTI measurements in various portions of the brain in MTLS patients.

6.2 REVIEW OF LITERATURE

Temporal lobe epilepsy (TLE) is the most common form of adult localization-related epilepsy and also the most common form of surgically remediable focal epilepsy, accounting for 60–75% of patients undergoing surgery for medically refractory epilepsy .Mesial temporal lobe sclerosis (MTS) is the major underlying cause of MTLE, and it is present in 60-70% of patients with MTLE who undergo surgery for treatment of medically refractory seizures.[4] Temporal lobe seizures are characterized by behavioral arrest and impaired awareness. Automatisms are common during the seizure, and include oral and/or manual automatisms. There may sensory (auditory), emotional (fear), cognitive (deja vu) or autonomic features (epigastric sensation, tachycardia, colour change) prior to onset of impaired awareness. Postictal confusion typically occurs.[5]

Jackson in the 19th Century was the first to link seizures characterized by a "dreamy state" to lesions near the uncus in the temporal lobe (hence the term "uncinate fits"). Gibbs and Lennox suggested the term psychomotor epilepsy to describe a characteristic EEG pattern together with emotional, mental, and autonomic phenomena for seizures originating in the temporal lobe. Gastaut proposed the term CPSs for partial onset seizures associated with loss of consciousness.[6]

Videotape and computer technology has permitted careful review of captured seizures and their associated EEG telemetry thus providing detailed descriptions of the features of temporal lobe seizures.[7] In the revised ILAE (Inetrnational League Against Epilepsy) classification, mTLE is under

"distinctive constellations/electroclinical syndromes" with the most common pathological substrate being hippocampal sclerosis.[8]

The electroencephalogram (EEG) of mesial TLE contains interictal features often associated with anterior temporal epileptiform discharges with a maximal voltage over the basal temporal electrodes.

Mesial temporal sclerosis (MTS), hippocampal sclerosis (HS), is the most common cause of TLE, representing greater than 80% and is the most common disease encountered in epilepsy surgery series and may be readily detected by brain magnetic resonance imaging (MRI) as mesial temporal sclerosis. Hippocampal sclerosis is a combination of atrophy and astrogliosis of the amygdala, hippocampus, parahippocampal gyrus, and the enterorhinal cortex. If isolated subfield involvement from HS occurs, mesial temporal sclerosis may be absent on neuroimaging results.[9]

Conventional electrophysiological and neuroimaging techniques sometimes fail to infer the location and/or the extension of the epileptogenic zone(EZ).[10]

In this context, neuroimaging techniques such as diffusion tensor imaging (DTI) can provide further insight into the pathophysiology of MTLE-HS.

Arfanakis et al. first reported reduced FA in the external capsule and corpus callosum in patients with TLE as compared to control subjects. Mean diffusivity and diffusion anisotropy of each selected structure were tested for correlations with age at onset and duration of epilepsy. Diffusion anisotropy was significantly correlated with age at onset of epilepsy in the posterior corpus callosum. Duration of epilepsy was not significantly correlated with the diffusion indices from any of the selected structures.[11]

Since that time many other groups have expanded on the extent of DTI abnormalities in the white matter of patients with TLE. Although there has been some degree of variability between the TLE studies, which likely reflects variability in patient populations and analysis techniques, what does appear to be clear is that TLE is associated with white matter abnormalities that are extensive and bilateral, in particular in patients with unilateral mesial temporal sclerosis (MTS).

Patients with TLE without MTS have also demonstrated DTI abnormalities of white matter, but there is some evidence to suggest that in TLE without MTS, DTI abnormalities are not as extensive and not as severe as in TLE with MTS. Concha L et al observed strikingly symmetrical bilateral abnormalities of axonal integrity in the fornix and cingulum in a series of patients with unilateral mesial temporal sclerosis. Their findings suggest that TLE with unilateral mesial temporal sclerosis is associated with bilateral limbic system pathology.[12]

There have been several studies demonstrating correlations between white matter DTI findings and duration of epilepsy. Govindan et al found that diffusion abnormalities associated with duration of epilepsy suggest progressive changes in ipsilateral uncinate and arcuate fasciculus due to chronic seizure activity.[13] Lin JJ et al investigated the integrity of two major frontal-temporal white matter association tracts, uncinate fasciculus (UF) and arcuate fasciculus (AF), and their clinical correlates in temporal lobe epilepsy. In subjects with TLE, the fractional anisotropy (FA) and apparent diffusion coefficient (ADC) of UF and AF ipsilateral to the side of seizure onset were abnormal when compared to healthy controls. Furthermore, lower UF FA

correlated with earlier age of seizure onset. This suggests that frontal-temporal white matter tracts are vulnerable to recurrent seizures and/or the factors precipitating the epilepsy.[14]

Some studies have failed to demonstrate a correlation between white matter DTI findings and duration of epilepsy. Thivard L et al explored the whole brain in order to determine if MTLE could have an impact on the organization and the architecture of a large cerebral network and to identify clinical factors that could mediate diffusion abnormalities. Identified three abnormal areas: an increased diffusivity was detected in the epileptic hippocampus and the ipsilateral temporal structures associated with a decreased anisotropy along the temporal lobe, a decreased diffusivity was found in the contralateral non-sclerotic hippocampus, the amygdala, and the temporal pole, and finally, a decreased anisotropy was noted ipsilaterally in posterior extratemporal regions. Duration of epilepsy, age at onset, and the frequency of generalized tonic-clonic seizures or partial complex seizures did not correlate with the presence of diffusion abnormalities.[15]

The demonstration of DTI abnormalities in the white matter of patients with TLE by a growing number of independent investigators strongly supports the validity of this finding.

6.3 AIMS AND OBJECTIVES OF THE STUDY

To study the Fractional Anisotropy and Mean Diffusivity of both hippocampi and various white matter tracts in

(i) Patients with temporal lobe epilepsy with MRI showing unilateral hippocmpal sclerosis,

(ii) Patients with temporal lobe epilepsy without evidence of Hippocampal Sclerosis in MRI, and

(iii) Normal controls

7. MATERIALS AND METHODS

7.1 SOURCE OF DATA

Patients with a clinical picture of temporal lobe epilepsy, referred to our department (opd/epilepsy clinic) and with EEG features of temporal lobe epilepsy undergoing MRI examination of brain.

Study Period from April 2019 – June 2020.

INCLUSION CRITERIA

Both males and females,

(i) with a clinical features and EEG consistent with temporal lobe epilepsy, and 3T MRI showing evidence of hippocampal sclerosis,

(ii) with clinical features and EEG features of temporal lobe epilepsy, but without any evidence of hippocampal sclerosis in MRI, and

(iii) normal controls (age matched).

EXCLUSION CRITERIA:

1. Presence of intraaxial structural abnormalities in locations other than temporal lobe, as it might interfere with the diffusion tensor imaging values.

7.2 METHOD OF COLLECTION OF DATA

This is a Prospective- Observational study.

Whole-brain Diffusion Tensor Imaging (DTI) will beacquired using Echo Planar Imaging.

We use Diffusion Tensor Imaging (DTI) and Statistical Parametric Mapping (SPM) to calculate rotationally invariant anisotropy and diffusivity maps and study objectively tissue organization in the 3 groups.

OUTCOME

Outcomes will be studied in the form of differences in the involvement of white matter tracts beyond hippocampus and will be compred among the 3 groups.

STATISTICAL ANALYSIS

All the continuous variables will be tested for the normality using Shapiro Wilk's test. Variables were normally distributed and expressed as mean ±SD. Categorical variables will be expressed either as percentage or proportion.

- Comparison of categorical variables (age) will be done by Chi -square test or Fisher's exact test based on the number of observations.
- Comparison of normally distributed continuous variables between cases and controls will be done by independent sample T test.
- Comparison of right and left sided variables within controls will be done by paired T test.
- All the P values less than 0.05 were considered statistically significant.
- Data entry will be done in MS excel worksheet.
- Data analysis will be done by SPSS software version 16.0

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY

Yes,

EEG

MRI Brain

7.4 HAS ETHICAL CLEARANCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

YES, Attached herewith.

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PROFORMA

S. No. **Epilepsy Clinic No.**

Hospital MRD. No.

Name:

Age:

Gender:

Marital status:

Educational Status:

Occupational Status:

Handedness:

Chief complaints:

Duration of seizure disorder:

Evolution of seizure disorder:

Semiological Description

Seizure type 1

Signature of Candidate

Signature of Supervisor

Seizure type 2

Antecedent history:

Relevant neurological history:

Family history:

Treatment history

Social and Personal History:

General physical and systemic examination:

Pulse: **Blood pressure:**

Other:

Signature of Candidate

Signature of Supervisor

Neurological Examination:

EEG (Routine/ Ambulatory/ Video EEG):

MRI Epilepsy protocol:

DTI MEASUREMENTS

Structure	Right		Left		Abnormal Side	Comment
	FA	MD	FA	MD		

Other investigations

FINAL DIAGNOSIS

Signature of Candidate

Signature of Supervisor

INFORMED PATIENT CONSENT

Date: _____

I.....D/o, W/o, S/o.....

.....am willing to participate in the study **"ROLE OF DIFFUSION TENSOR IMAGING IN MESIAL TEMPORAL LOBE EPILEPSY"** The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason.

.....
Signature of the Witness

Name:

.....
Signature of the patient

Signature of Candidate

Signature of Supervisor

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____

निवासी _____

इस शोधकार्य "**ROLE OF DIFFUSION TENSOR IMAGING IN MESIAL TEMPORAL LOBE EPILEPSY**" में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____ _____

गवाह के हस्ताक्षर रोगी के हस्ताक्षर/अंगूठे का निशान

नाम: नाम:

_____

अन्वेषक के हस्ताक्षर

_____

विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ_____

ਵਾਸੀ _____

"ROLE OF DIFFUSION TENSOR IMAGING IN MESIAL TEMPORAL LOBE EPILEPSY" ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

_____ _____

ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____ ਮਿਤੀ_____

ਪਤਾ _____ ਪਤਾ _____

_____

ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

_____

ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ